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MEDICINAL AGENTS

OF THE

1893. FABRIK-MARKE 1893.

TRADE-MARK

CHEMICAL WORKS

(vorm: E. Schering),

BERLIN.

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OF THE

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PREFACE.

The discovery of the DAGUERRE method of producing pictures of natural objects—in other words, the invention of the art of photography—gave an important stimulus to the preparation of chemicals in a high state of purity, and indirectly exerted an influence upon the synthesis of organic compounds. The importance of the art was recognised by ERNST SCHERING, founder of the Chemische Fabrik auf Actien, who set himself the task of preparing the chemicals used in it in a condition of the utmost purity. In thus sketching in barest outline the origin of the firm, allusion may be made to the historic interest that gathers round the design impressed upon the title-page and cover of the volume. Though by no means a conspicuous figure, it is associated with the earliest history of the Fabrik, and has more significance than appears at first sight. Those readers acquainted with alchemic lore and symbols will recognise the superimposed forms representing fire and water as well as the central circle which stood for the third of the "elements" of the ancients. The part played by the sun as a source of energy in chemical processes is symbolised by the halo of rays streaming from the "star," while the particular application of this curious group of signs to the firm is indicated by the initials (E.S.) of the founder.

This may be regarded as the commencement of the manufacture of fine chemicals by this firm, which has now attained the dimensions indicated by the number of products described in the following pages—products which are, with few exceptions, all of recent introduction.

From the preparation of well-known compounds in qualities distinguished by their high purity to that of entirely new bodies of definite chemical nature was a natural transition. The development of synthetical organic chemistry revealed new and better methods of procedure, which were promptly investigated and taken advantage of in the works, and the inevitable result of the progressive tendency always kept alive was that the firm of E. SCHERING occupied the foremost place among those chemical manufacturers engaged in the production and investigation of new remedies.

It is noteworthy that the very first of the synthetical remedies—Chloral Hydrate—was prepared in the chemical works of the firm, and the prestige conferred by this achievement was again enhanced by the introduction of Salicylic Acid. It may be remarked, in passing, that although since the *début* of these compounds the class of synthetical medicinal compounds has enormously increased, they still maintain their high position in *materia medica*, and, indeed, have become almost indispensable in modern therapeutics.

It will be seen that the derivative of chloral, Chloralamid, rivals the mother-substance in general importance, and in

certain cases is preferable to it. The steadily-growing literature of the compound establishes its valuable hypnotic properties and the freedom of its medicinal action from unpleasant after-effects. This latter feature has attracted general attention; to it is largely due the great strides which Chloralamid has made in the favour of medical men in all countries.

The monograph on Piperazine, the first remedy in the gouty diathesis which organic chemistry has yielded, should prove especially interesting. Although so recently introduced, the peculiar chemical and chemico-physiological behaviour of the base, especially in relation to uric acid and its compounds, has procured for it a searching investigation and extensive trial which enable a sound judgment as to its value to be already formed. When combined with Phenocoll it seems to form the most efficient remedy for the various forms of gout which has hitherto been discovered.

The noteworthy points in the therapeutical uses of Phenocoll are its comparatively ready solubility in water, and its freedom from any deleterious action on the blood or circulatory system generally. The medical practitioner will not need to be reminded that the possession of both these properties gives Phenocoll a marked advantage over all other remedies of the same class.

Finally, the attention of the reader may be directed to the chapters on Diabetin, Strontium Salts, and Thiosinamine,

the latest comers among therapeutical novelties. It is not possible, of course, to predict with certainty what position these substances will finally attain in *materia medica*; but it may at least be said that they give promise of winning recognition as real enrichments of the physician's armament against disease.

Chemische Fabrik auf Actien
vormals E. Schering.

BERLIN,
February, 1893.

PIPERAZINE.

An interesting paper was read in Berlin some months ago by Finzelberg, which illustrates the chain of events by which Piperazine was discovered and its therapeutical value established. It appears that the father of the chemist just named died from uræmia caused by renal stone, and this led his son to resolve to find, if possible, a substance that by internal administration might either prevent the formation of deposits of uric acid or effect their solution when formed.

Consultation with other chemists as to the most likely means of effecting this end led to a determination to experiment with all the known organic bases, as regarded their solvent action on uric acid, in the hope of discovering one that would produce the desired result without producing any deleterious or toxic effect upon the organism.

Several years passed by during which the investigation was carried on as opportunity presented, until general attention was directed to the natural base, spermine, and to the synthetically prepared diethylenediimine of Ladenburg, by the work of Schreiner and Professor Poehl.

At first spermine and Ladenburg's base were believed to be identical, but the different appearance of their bismuth iodide compounds under the microscope convinced Schmidt and Majert that they were different bodies. A purer preparation of the synthetical compound named Piperazine—a designation indicating its relationship with piperidine, piperine, and pyrazine—was subjected to careful investigation, the upshot of which was the discovery of the remarkable properties detailed in the following paragraphs.

PHYSICAL AND CHEMICAL PROPERTIES.

Piperazine is represented by the formula $C_4 H_{10} N_2$. Crystallised from water it assumes the form of glassy lustrous tables. When

exposed to the air it is deliquescent, the crystals rapidly absorbing carbon dioxide and water, and becoming liquid. When subjected to the action of heat it melts between 104° and 107° C., and boils at 145° C.

The compound is very readily soluble in water, forming an almost tasteless, strongly alkaline but non-caustic solution.

Hydrochloride of Piperazine, a salt of the base which has also been used therapeutically, forms silky, lustrous, lanceolate crystals, very easily soluble in water and, with more difficulty, in alcohol.

The most important chemical property of Piperazine is its power of combining with a large proportion of uric acid, forming urate of Piperazine, a salt distinguished by its ready solubility in water. Even in the presence of an excess of the acid only the neutral salt is formed.

The clearest idea of the action of Piperazine as a solvent of uric acid is obtained by comparing it with that of lithia, the remedy chiefly resorted to, prior to the discovery of the synthetical base, in the treatment of uric acid diathesis where the primary indication was to effect the solution and elimination of uric acid. Now when brought together in the cold with aqueous solution of the acid, Piperazine dissolves twelve times as much as the same weight of carbonate of lithium under similar circumstances. Further, the salt formed by the organic base was found to be much more soluble in water than urate of lithia; the latter requires 368 parts of water for solution, while one part of Piperazine urate is taken up by 50 parts of water.

A number of observers have examined the chemical activity of Piperazine as a solvent for uric acid, especially when in the form of those concretions which, originating in the renal pelvis and bladder, give rise to severe pain and other serious symptoms.

Dr. Finzelberg subjected to the action of Piperazine, urinary calculi, consisting either of pure uric acid, or of that compound together with ammonium urate, calcium phosphate, etc. He found that all these forms of concretion dissolved freely and perfectly within a comparatively short time in a one per cent. Piperazine solution. In some cases nothing remained but a light honeycombed skeleton, which consisted of the hardened cementing mucus. It was particularly

striking that the edges of the calculi, sometimes very sharp, dissolved away rapidly in the Piperazine solution.

A similar research was carried out by Drs. Biesenthal and Schmidt. The "stones" they had for experiment consisted of uric acid (or urates), or were of a composite nature, being made up of alternate layers of uric acid and calcium oxalate or phosphate. The authors recorded the observation that even large compact pieces belonging to the first class, dissolved with extraordinary readiness in a solution of Piperazine.

One series of experiments was especially interesting as showing the comparative activity of Piperazine, sodium carbonate, lithium carbonate and borax, in effecting the solution of uric acid stones. A "tophus" was obtained of great hardness, made up of concentric layers of uric acid. Cubical pieces, of as near as possible equal weight, were sawn from this, and each suspended by means of test-tubes with fine perforations at the end, in one per cent. solutions of Piperazine and of the salts enumerated above. All the solutions were kept at blood-heat and under exactly the same conditions. The results of the experiment are shown in the following paragraphs :—

1. Piperazine Solution.—Two and a-half grns. of the stone, after only six hours, was all dissolved save a scarcely perceptible residue without stratification. The solution had become yellow in consequence of the organic matter which had also passed into solution.

2. Lithium Carbonate Solution.—Three grns. of the stone was not dissolved after 48 hours, a compact skeleton being left, in which fine stratification was clearly recognisable. This residue was removed to the Piperazine solution, where, with the exception of a few scarcely visible flocks, it had soon all dissolved.

3. Sodium Carbonate Solution.—After 48 hours immersion in this, a fragment of the stone weighing 2¼ grns. was unaltered in bulk. A white crust of sodium acid urate had formed on the stone, which, though at the most $\frac{1}{50}$th of an inch thick, prevented any further action of the soda solution. Beneath the

white coating, the stone was as hard as ever, but transferred to the Piperazine solution it dissolved in a few hours.

4. Borax Solution.—A fragment weighing ½ grn. only dissolved after a digestion of 20 hours, and then the same compact skeleton was left behind, as with lithium carbonate. It rapidly and entirely dissolved in Piperazine, save a few scarcely perceptible flocks.

The capability shown by the solution of Piperazine of dissolving a part of the organic substances, which enter into the composition of these stones, explains the rapidity with which they are broken down and pass into solution when digested in it.

Experiments with other stones confirmed the observation of Finzelberg that, long before complete solution takes place, sharp edges are broken down and the concretion assumes a slippery character. It is shown later that every feature of the behaviour of tophi with Piperazine solution has been of significance in determining the therapeutical application of the compound.

Drs. Biesenthal and Schmidt also carried out in the chemical laboratory a series of experiments on the comparative diffusibility of the urates of Piperazine, sodium and lithium through animal membrane. The results demonstrated that Piperazine urate diffused more rapidly than either of the other salts. This observation has also therapeutic significance in view of the important part which osmosis is known to play in nutritive and other processes in which the tissues are concerned.

Among the experiments performed by Biesenthal and Schmidt was the following:—

A solution of Piperazine hydrochloride was placed in a fractionating flask, provided with a small separating funnel, and the side tubulure of which dipped into the bulb of a second similar flask containing barium hydrate solution; both the flasks were joined up with air-tight fittings, and exhausted. Soda carbonate solution was allowed to fall through the funnel, and the apparatus again made completely vacuous. On warming the mixture to 40° C. (104° F.) and constantly shaking the barium solution, the latter gradually became turbid, and a thick layer of barium carbonate formed.

These phenomena were due to the double decomposition of sodium carbonate and Piperazine hydrochloride with the formation of sodium chloride and Piperazine carbonate, which latter, on warming, gave off carbon dioxide.

The bearing of this experiment upon the behaviour of Piperazine in the organism is evident; it becomes largely converted into hydrochloride in the stomach, and this salt is brought into contact with sodium carbonate in the alkaline juices of the tissues.

But it would be equally important to the efficient action of Piperazine as a solvent of gouty secretions that the urate should not undergo double decomposition with the sodium carbonate of the alkaline juices; if this were the case Piperazine carbonate and the relatively insoluble sodium urate would be formed and the latter re-deposited.

In order to test this question the authors above-named arranged two fractionating flasks again as in the experiment just described. In the one was placed 400 cc. of a solution of 24 grns. of Piperazine with 45 grns. of uric acid (from which all possible traces of carbon dioxide had been removed by long boiling). The other contained barium hydrate solution as before. The flasks were again exhausted, soda carbonate solution introduced, and the whole system heated to 40° C. No trace of turbidity appeared, however, in the barium solution, thus showing that no decomposition occurred and no Piperazine carbonate was formed in the flask under conditions closely approximating to those which obtain in the human body.

TESTS.

In order to ascertain the precise manner in which the remedy is affecting the excretory functions, and to enable the physician to control its action, it is necessary to be able to trace Piperazine in the excretions, and particularly in the urine. The method of doing this is as follows:—

About 10 ccm. of the urine to be examined for Piperazine is decomposed by few drops of concentrated soda and slightly warmed

for a short time. After cooling the liquid is filtered from the flocculent precipitate of phosphates, etc., made decidedly acid by few drops of hydrochloric acid (avoiding any large excess) and treated with a solution of potassium-bismuth iodide.

The first effect is the formation of a dirty-coloured amorphous precipitate which contains no Piperazine, but is produced by nucleo-albumen, a constituent of normal urine. The mixture is warmed for a short time to about 40°—50° C., in order to cause the precipitate described to aggregate, and then rapidly cooled and filtered. On energetically rubbing with a glass rod, a pomegranate-red crystalline compound appears in microscopic needles which assume a distinctive arrangement.

When the proportion of Piperazine present is too small to be detected in this way, another more refined *modus procendi* is available :—

The urine is made decidedly acid and evaporated; a tenacious brown residue is left behind which is rubbed down with caustic soda in powder. The evolution of ammonia which occurs is due to the decomposition of the urea. The mass is then mixed with about an equal weight of sand and rapidly distilled in a retort with an efficient condenser until no more water-vapour passes over. The Piperazine present in the urine passes over in the distillate unchanged, but organic nitrogenous bodies like sarcosin, creatine, and xanthine are decomposed. The liquid, which collects in the receiver, has a strong odour of alkylamines, is boiled for a short time in order to get rid of the greater part of the ammonia, filtered, acidified with hydrochloric acid, and tested with the double iodide solution referred to already.

A convenient but less striking process depends upon the characteristic crystalline form of benzoyl-piperazine. Phosphates are separated as in the first process outlined above, a drop of benzoyl-chloride is added, and the whole powerfully agitated. After standing half a day the dirty-white sediment is thrown on to a filter and extracted with absolute alcohol; the extract is evaporated on a watch-glass, and a drop of the concentrated liquid examined under the microscope. The benzoyl compound of Piperazine separates in characteristic transparent rhombs of great regularity.

PHYSIOLOGICAL ACTION.

It has been already intimated that Piperazine was at first supposed to be identical with the "Spermine" of Drs. Brown-Sequard and Poehl; hence it was primarily regarded as a nervous stimulant.

The earliest physiological examination of Piperazine was carried out by Prof. Kobert of the Dorpat Pharmacological Institute. The result was to demonstrate the freedom of the compound from any injurious or poisonous action. At the same time no evidence was obtained of the stimulant action upon the nervous system anticipated. Similar results were obtained by Bock, who concluded that Piperazine did not possess any marked physiological action.

Light was thrown upon this apparent discrepancy by the discovery that there was no identity between Piperazine and spermine. Then attention was directed to the solvent power of the synthetical base for uric acid, and on this property was based its employment in medicine.

Dr. Vogt, in conjunction with the chemists Ferdinand Vigier and Gautrelot, investigated the effects which Piperazine produces upon the metastasis or tissue change continually going on in the animal body. They confined their attention to the urine of patients undergoing treatment with the synthetical compound. The excretion was examined two days before the administration, then after the substance had been given three days and again two days after its use had been discontinued.

The results of this work led the authors to conclude as follows:—

1. That the percentage of urea in the dry residue had fallen about a sixth during the treatment, but that it was higher two days after the administration was discontinued than before it was begun.
2. That the percentage of uric acid had decreased after three days of the treatment, and still more so two days after suspension.
3. That the ratio of uric acid to urea also fell steadily and continuously during the period of observation.

The interesting results are noteworthy, though they have not received confirmation by other workers. As a matter of fact our knowledge of the influence of Piperazine on metastasis is still far from complete. It is appropriate that mention should be made here of the experiments which Drs. Heubach and Kuh made upon themselves with Piperazine. Taking as much as 2½ grammes daily they did not observe any functional disturbances or any ill-effect upon the general well-being, but in every experiment a slight increase was observed in the amount of uric acid excreted.

Drs. Biesenthal and Schmidt (*Berl. klin. Wochenschr.*, 1892, January) turned their attention also to the harmlessness of Piperazine when given internally. Daily doses of 15 to 45 grns. gave rise to no kind of disturbance, and in some cases the compound was taken in ounces at this rate without any unpleasant symptoms appearing. Further, they convinced themselves that much larger doses even than these of Piperazine could be given without any undesirable albuminous changes occurring. This was proved by experiments on a healthy man, under strict diet, to whom during six days 1½ drms. of Piperazine was given, and whose urine was carefully examined day by day. The urine maintained its acidity, but after the use of Piperazine this considerably diminished; the base was always present in the urine in large quantities.

Further, it was of course necessary that such a remedy intended for the solution of gouty concretions in the human tissues, should be stable, as if split up during its passage through the organism, it would be of no use as a solvent for uric acid deposits. It has, however, been shown that such stability is possessed by Piperazine (*Ber. d. D. chem. Gesell.*, 1891, pp. 243 and 3237). After a single dose of 75 grns. by far the greater part is excreted with the urine in the course of 24 hours, but even after six days the presence of Piperazine can be detected in the urine, which would not of course be the case if it underwent decomposition in the body.

It was one object of the research of Drs. Biesenthal and Schmidt to trace Piperazine in its course through the digestive organs and the circulatory system, until it arrived at the point where gouty deposits had been formed.

They stated that when the base enters the stomach it is converted, largely at least, into a hydrochloride. This salt, with the sodium carbonate of the alkaline juices, undergoes double decomposition, sodium chloride and Piperazine carbonate being formed. They experimentally demonstrated the mutual decomposition of Piperazine hydrochloride and sodium carbonate when brought into contact (*v.* under "Chemical Properties"). Piperazine carbonate has a solvent power for uric acid similar to that of the base, and coming in contact with the gouty deposits forms Piperazine urate, a compound which is more stable to a marked degree than the hydrochloride, as shown by the experiments of Biesenthal and Schmidt, detailed in the previous chapter.

MEDICINAL PROPERTIES AND USES.

From the time of Pliny downwards, attempts have been made to effect the solution of urinary stones by chemical means—that is to say, by the administration of agents which were believed to exert a solvent action upon the concretions. This treatment was, however, first placed upon a rational basis by the researches of Fourcroy and Vauquelin, who proved that the stones were dissolved by alkalies if consisting of urates, and by acids when made up of phosphates.

There has, however, always been the difficulty to contend with, that substances used in the laboratory with success, proved of little value when used clinically, because they underwent changes in the organism and reached the seat of the disease in altered, and, for the purpose in view, inert forms. Carbonate of lithium, for instance, which formed the most soluble compound of uric acid known prior to the introduction of Piperazine, appeared in the urine mostly as insoluble chloride.

Other authors, such as Pfeiffer and Posner, tested the effect of various remedies upon the solvent power of the urine for uric acid, both pure and in the form of stones and gravel. With all these remedies, it was observed that so long as they were used the uric acid decreased, but as soon as they were discontinued, the proportion of acid rose again.

A further disadvantage of these earlier remedies was that neither the stomach nor the bladder was capable of bearing the quantity of alkali necessary for the solution of the concretions, while this class of substances had other serious disadvantages. For instance, if given in too large quantities, so that the urine became unmistakably alkaline, phosphates were thrown out of solution and formed secondary layers, increasing the size of the stones already formed.

Altogether the internal treatment of phosphate stones has been associated with great difficulties. Injection of acid solution has sometimes proved effective, but by that method alone their formation cannot be prevented. This could only be done by assiduous catheterisation, drainage and washing out of the bladder, so as to prevent the ammoniacal fermention of the urine.

Unfortunately the alkalies do not attack the organic foundation of the stones, and, although theoretically the solution of a vesical stone is conceivable enough, experience has not hitherto been able to record a single well-authenticated case in which such an effect has been attained in the human body. When sometimes physicians and patients have believed that the use of such solvent remedies had improved the disease, this was due either to a beneficial effect upon associated symptoms (*e.g.*, vesical catarrh) or to a spontaneous effort of nature.

Under these circumstances it should not excite surprise that the introduction of a compound possessing such remarkable powers of dissolving uric acid as Piperazine should have at once attracted attention.

At the same time it must be noted that vesical and renal calculi are not generally of the same composition chemically; vesical "stones" consist almost always of calcium phosphate, or, more rarely, oxalate, with the exception of the small nucleus that is always present, while renal stones much more frequently are composed nearly entirely of urates, though sometimes mixed with phosphates and oxalates also.

Any foreign body in the bladder may form the nucleus of a calculus, especially if the patient's urine be loaded with phosphates or urates. A small renal calculus may, of course, figure as a vesical stone by subsequent deposition upon it of phosphates, oxalates, etc., unless it

be passed away with the urine immediately after arriving in the bladder.

Further it is believed that the formation of both vesical and renal calculi is accelerated by the continuous imbibition of large quantities of strongly alkaline mineral waters; these agents, in neutralising the urine, give rise to eminently favourable conditions for the formation of concretions.

In considering the extensive literature which has accumulated on Piperazine, it will be convenient to give attention first to its employment in troubles of the urinary tract due to the formation of concretions of the solid constituents of the urine.

IN RENAL AND VESICAL CALCULI, ETC.

(*a*) Internally.

Although Dr. Vogt made a special study of the physiological behaviour of Piperazine, he also records its employment clinically in cases of gravel (gouty) associated with severe renal pain. After the administration of Piperazine had been continued a few days the pains entirely ceased, and the urine gave evidence of an increase in the amount of urea excreted, with a corresponding decrease in the amount of uric acid.

Though the first diagnosis turned out to be incorrect, yet a case of presumptive gravel which came under the observation of Drs. W. Ebstein and C. Sprague (*Berl. klin. Wochenschr.*, 1891, No. 14) should not pass without mention. The principal symptoms were cystic spasm, local pain during urination and obscure transient pains in various parts of the body. Piperazine was given in doses of 30 to 45 grns. daily for a fortnight, during which the patient was strictly dieted, and the urine daily estimated for total nitrogen and for uric acid.

It was found out later, that the urinary troubles of the patient were due to a vesical ulcer, but the case is of interest as showing that Piperazine may be given in considerable quantities for prolonged periods without producing any disagreeable effects, even when the epithelial coating of the bladder was the seat of a morbid process.

One of the cases described by Dr. Bardet, Paris, was of renal colic. In the course of six days 75 grns. of Piperazine pur. were given. The patient had had an attack of colic the day before the medicament was begun. The treatment was followed by rapid excretion of small renal stones, and the patient stated that micturition was more rapid and easy than usual.

Drs. Heubach and Kuh had among their patients a man of 37 who suffered from renal colic; there was constipation, difficult urination, urine with much sediment and some albumen. After a week's treatment with the usual routine remedies, one tablespoonful of a ½ per cent. solution of Piperazine every two hours was prescribed. On the third day of the treatment, violent pains in the region of the left kidney appeared, which increased during defæcation. A little later a uric acid concretion was passed with great pain and slightly bloody urine. The "stone" resembled in size and form a medium incisor tooth and weighed six grns. The surface bore signs of corrosion. Since the passage of this stone the symptoms did not reappear.

In a second case, gravel, consisting chiefly of uric acid, had existed for years with frequent attacks of colic and hæmaturia. A tablespoonful of the ½ per cent. Piperazine solution every two hours was prescribed, and after the treatment had been continued ten days there was an abundant discharge of small round uric acid concretions. This lasted for several days and was followed by a cessation of the colic and hæmaturia.

In a lengthy treatise on the treatment of the uric acid dyscrasia by internal medication in general, and by Piperazine in particular, Dr. Brik (*Wien. med. Blätter*, 1891, December) describes a case of an old man who had suffered for 45 years from uric acid sediments. The alkaline method of treatment had been chiefly followed, but this was not successful in preventing for long the precipitation of uric acid. The patient had been operated on for stone more than once, very large concretions being removed each time.

Piperazine was prescribed in daily doses of 15 grns. The first effect was increased diuresis and a manifest diminution of sediment. The urine was always acid in reaction. As the Piperazine was con-

tinued the uric acid sediment disappeared altogether, and did not again reappear in notable quantities for four weeks. A few days' use of the remedy was sufficient to again free the urine from excess of the acid.

The same author had under treatment a boy of 14 years with enuresis nocturna, for which a variety of treatment had been tried during two years, but without success. The specific gravity of the urine was 1·027, its reaction strongly acid, and 0·2 per cent. of albumen was present. It deposited a sediment of uric acid in different forms (such as are constantly seen in incipient *calculosis renalis urica*) and also containing red and white blood-corpuscles and epithelial scales. The urinary tract showed nothing abnormal.

Diagnosing the enuresis as due to incipient calculus formation, the author ordered 15 grns. of Piperazine in six ounces of water, to be taken in two days. From the second day the incontinence ceased, and did not appear again during four successive nights, although the medication was not repeated. Although the patient was not quite cured, the result was characterised as exceedingly satisfactory, the enuresis showing itself only once a fortnight or three weeks.

The combination of diabetes and uric acid dyscrasia presented special difficulties under the ordinary methods of treatment. Such a case was also recorded by Dr. Brik. The daily quantity of urine was between five and seven pints, albumen was present in traces, sugar to the extent of one to three per cent., and uric acid in large quantities. After other remedies had been tried without success, Piperazine was prescribed. The proportion of uric acid considerably decreased, and for some time sank to zero; subsequently it rose again to a high level, to drop once more to nil after a few days.

In this case, and another of similar nature, no effect was observed upon the excretion of urine and sugar, but the subjective well-being was markedly improved and the accompanying joint pains disappeared. The second diabetic patient referred to had also acetonuria, but this abnormality was soon entirely removed. Without entering into further detail, the author mentions that very similar results were obtained in six other cases of excessive excretion of uric acid.

Dr. Brik spoke of Piperazine as the best uric acid solvent, and warmly recommended it, especially in the treatment of renal calculus and in the various nervous disturbances which follow on such affections. When vesical stones were very large he considered it advisable to operate and then combat the uric acid dyscrasia with Piperazine, in order to prevent the re-formation of the calculi.

Dr. Schott, Philadelphia, had also under his care a case of renal colic in which repeated hypodermic injections afforded only partial relief. The attacks recurred day after day, and were exhausting the patient's strength. In consequence an operation was proposed when on the eighth day, unexpectedly, the cause of all the trouble was passed in the form of a fair-sized stone.

Potash and lithium salts had been used with very little benefit, and the author ascribed the fortunate issue of the case to the prescribing of solution of Piperazine. The patient himself was also very enthusiastic about the remedy and the relief which it afforded him. Dr. Schott added (*Notes on New Remedies*, 1891, Dec.,) that since attaining this favourable result he had prescribed Piperazine in other similar cases.

An interesting case is reported by Dr. Pfeiffer, Wiesbaden. The patient, a lady, suffered from violent pains in the region of the kidneys extending along the course of the right ureter to the upper part of the thigh. There was also observed in the right iliocaecal region a marked swelling, and the urine, passed in very small quantities at a time, had a bright yellow appearance. When microscopically examined it revealed the presence of a great quantity of flocculent mucous matter with a number of epithelial cells. Although the examination was repeated daily, no crystals of uric acid could be discovered, and in the first instance the diagnosis was felt to be difficult, but Dr. Pfeiffer concluded that uric acid and urate concretions were the cause of the mischief, and acting on this belief he began a course of treatment with Piperazine.

Before the course was begun, an attack of sickness came on, and fever also developed; the local pain increased to a very great extent, so that the patient was unable to get quiet rest at night, in spite of large doses of morphine hypodermically. All the usual uric acid solvents—lithium carbonate, alkaline waters, etc.—had been tried without success.

Piperazine was ordered in daily doses of 15 grns. in aqueous solution. After the treatment had been continued four days a number of fragments of uric acid were to be detected in the urine by the naked eye. The administration of the remedy was also followed by diminution of pain and fall of the febrile temperature to the normal level, while the general condition of the patient improved, and rest and sleep were obtained without difficulty. The hard swelling also diminished and local pain practically ceased.

These results were taken as evidence of the correctness of the diagnosis, Piperazine having rapidly effected the solution of concretions impacted in the right ureter which the older remedies had failed to move. Three daily doses of 15 grns. so far effected solution of the concretion that the disintegrated fragments could pass into the bladder.

The patient was kept on 8-grn. doses *pro die* of the remedy, with the result that the amount of uric acid excreted gradually diminished to zero.

In previous cases of "stone" treated with the ordinary remedies, Dr. Pfeiffer had always observed, on about the eighth day, a large increase in the volume of urine, which then became loaded with uric acid concretions, and assumed a marked red colour.

In the case treated with Piperazine, the peculiar red colour did not appear. This he explained as due to the fact that the synthetical base not only dissolved the uric acid, but the mucous and other matter which held the constituents of the "stone" together.

This property of Piperazine of dissolving the organic cementing material of urinary concretions, enables it, according to Biesenthal, to disintegrate stones consisting almost entirely of calcium phosphate. At the same time, it has the advantage of not rendering the urine alkaline, and so leading to phosphatic deposits.

Dr. Biesenthal believed that the continued treatment of patients suffering from the symptoms of uric acid dyscrasia, by large doses of alkalies, was very risky—an opinion which received confirmation in the examination of a renal calculus taken from a patient who had been treated for a prolonged period with an alkaline mineral water. The calculus had only a small nucleus of uric acid, around which a fairly thick deposit of calcium phosphate had accumulated.

The author had met with 47 cases in his own practice, and collected from colleagues the details of 220 more, in which Piperazine had been employed with extraordinary success. Cases of renal colic were included as well as various hæmorrhages from the ureters; some of the latter, even when they had existed for years, were completely relieved by the use of Piperazine.

Dr. Volmer obtained specially gratifying results in the case of a merchant who had suffered for a prolonged period from renal colic. He had been through a course of alkaline waters, and concretions were passed which contained uric acid. In spite of this relief and continued treatment with ordinary remedies, fresh attacks of colic appeared, followed in every case by hæmaturia of several days' duration.

Piperazine was given in doses of 15 grns. (combined with an equal weight of Phenocoll), and after this dose had been maintained for four weeks, the quantity was reduced one half. From the very first the local symptoms improved, and the hæmorrhage ceased to recur.

Excellent results in renal colic were also obtained by Professor Schweninger, the diet and excretions of the patient being so regulated as to hinder the formation and separation of uric acid in the system.

(*b*) By Local Irrigation.

Attention was called early in the history of Piperazine to its freedom from caustic or irritating properties; the special significance of this fact lay in the possibility it opened up of applying Piperazine in solution locally, where vesical stones had to be treated. It has been already pointed out that not only are the alkalies inefficient solvents when used in this way, but also that the bladder is incapable of bearing the quantity of alkali necessary for the purpose.

Dr. Brik specially noted the suitability of Piperazine for injection into the bladder, owing to the fact that it does not display any local irritant action. Drs. Biesenthal and Schmidt used for irrigation of the bladder one and two per cent. solutions, these being borne for prolonged periods without the slightest difficulty. Other observers found that even five per cent. solutions could be borne without difficulty; it

was believed that the necessary renewal of the solution surrounding concretions would be brought about by the movements of the patients.

In this particular direction there is a field for the initiation of a new method of treating vesical stones, which promises to be of excellent service. At any rate the injection of solutions of Piperazine is worthy of trial, both before proceeding to operative measures and afterwards with the view of preventing the recurrence of the difficulty.

Summing up the unique properties which Piperazine displays in the treatment of affections of the urinary tract due to uric acid dyscrasia, it appears that:—

1. Piperazine dissolves concretions not only of uric acid but also of phosphates, etc., in consequence of its power of disintegrating the mucous or albumenoid cementing-material which binds them together.

2. Piperazine relieves renal colic and other local pain associated with the formation of concretions in the urinary tract owing to its power of dissolving the sharp edges of calculi and giving them a slippery character.

3. As a consequence of the effect indicated above Piperazine determines the evacuation of "stones" from the kidneys, ureters, or bladder, very soon after administration and before time has elapsed for complete solution.

4. Piperazine is not only superior as a solvent of uric acid and urates to all previous remedies, but also is free from their disadvantages.

5. Piperazine does not render the urine alkaline and so favour the deposition of phosphates.

6. Being free from caustic or irritant action, Piperazine has been used successfully and without any ill-effects for the irrigation of the bladder in the treatment of vesical stone.

II.—IN THE GOUTY DIATHESIS.

It should be scarcely necessary to premise that medication alone can scarcely be expected in every case to effect alone the cure of

gout. The affection is characterised by marked obstinacy to all forms of treatment, and further there are factors in its etiology or causation which have to be taken into account in combating its symptoms.

Among these factors an important part is played by diet and habits of living, and it is a well-recognised principle in the therapy of gout that dietetics are almost equal, in the possibilities of improvement they offer, to more purely medicinal measures.

Further it would seem to be necessary to point out that when a patient has suffered for years from the gouty diathesis, when the whole system is more or less saturated with excess of uric acid and other abnormal constituents, it cannot be expected that a few doses of any medicament, however powerful in action, will be sufficient to effect a complete and permanent cure.

The pathological distinction between rheumatism and gout in their pure forms is tolerably clearly defined, but there is a large proportion of cases in which it is difficult to diagnose with certainty whether they are rheumatic or gouty in nature. It is in such forms of "rheumatic arthritis," as they are termed, that a trial with Piperazine is specially recommended by the authors who have written upon the properties and employment of the base. Sufferers from the uric acid diathesis and its numerous sequelæ fill the various watering places of Europe, and are recommended to bathe in the alkaline waters, and to take a certain quantity of them internally.

This treatment is, of course, not within the means of all, and it has been, therefore, emphasised as a marked advantage of Piperazine that a course can be gone through without leaving home or temporarily abandoning the usual avocation. At the same time, as will be seen from the following recorded cases, the newer remedy is superior in efficacy to those hitherto employed.

The effects of the administration of Piperazine may be watched and compared from time to time by examining the urine of patients periodically for urate of the base, by the methods described in a previous section. In this way the activity of the remedy in determining the elimination of the excess of uric acid in the fluids of the body may also be estimated.

Dr. Bardet tried 15-grn. doses of Piperazine in the case of a woman suffering from gout, in whom the urine was heavily loaded with urates. In the course of two days the urine cleared up, while the author was able to detect a slight decrease in the amount of uric acid present within 24 hours of beginning the treatment.

In a second case a gouty patient suffered from an ulcer of the elbow. The first two days of the treatment 1—1½ grns. of Piperazine were given daily (by injection) and afterwards 3—6 grns. every two days for a week. The patient observed that the ulcer and redness, which circumscribed it, rapidly decreased simultaneously, while, further, pain was promptly lessened in intensity. The proportion of uric acid in the urine was 0·65 before the treatment and 0·52 on the last day of it.

Another man had gout of long standing and podarthritis. He had been subject to intermittent attacks for five months and had rarely been free from pain for two days together. Injections of 3—5 grns. of Piperazine (hydrochloride) were made every two days in the nates. Alleviation of pain was experienced after two days of the treatment.

An exudation of inflammatory secretion from enormous swellings of the joints produced by urates was a conspicuous symptom in a second case of podarthritis, where extensive and unusual deformity in the limbs had been produced by the disease. The treatment adopted was to inject 3—5 grns. of Piperazine or 1 to 1½ grns. of the hydrochloride every second day. The patient affirmed that the injection facilitated and accelerated the excretion of urates through the skin.

The following brief histories of four cases are from a lengthy treatise by Drs. Biesenthal and Schmidt, on their clinical experience with Piperazine (*Berl. klin. Wochenschr.*, 1892, No. 2).

The first was of a man 57½ years old, in whom gout was hereditary, and who had suffered numerous attacks and undergone a number of different treatments. During February and March of 1891, about 150 15-grn. doses of Piperazine were given, and during that time gravel and stones, often as large as a small bean, were discharged, almost daily. In July the treatment was suspended for a time, when new outbreaks occurred, and Piperazine was again resorted to and kept up for about six months; the joints, which had been severely

affected, gradually regained their normal size, the only abnormality remaining being a slight painful swelling of the right ankle. The patient was able to walk about, and felt well.

Another man, of 35 years, came from a family which had been gouty through the two preceding generations. He had about two attacks each year, varying in duration from one to three weeks; both large toes and the adjacent tissues were the seat of gouty deposits. The preparation known as Gout Water (*v.* p. 43 *et seq.*) was prescribed and continued till about 30 bottles (each containing 15 grns. of Piperazine) had been taken. Some months after the discontinuance of the treatment a slight attack of gout appeared, but this was entirely cured by a single day's use of the water.

A striking illustration of the prompt action of Piperazine is afforded by the following case. The patient, a man of 43—not hereditarily predisposed—had attacks of gout usually in spring and autumn, which obliged him to keep to his bed for a week or fortnight. In December of 1891, an exceedingly severe attack set in, for which four grns. of Piperazine were taken, followed by 12 grns. the next morning, and 15 grns. on the third day. Immediately after this last dose the condition of the patient was so much improved that he could get up and walk out; the swollen and reddened joints reassumed their normal colour and appearance. After 18 daily doses of 15 grns. of Piperazine, every symptom of the attack had passed off, and the treatment was stopped.

Hereditary predisposition was similarly lacking in the next case, a gentleman of 65 years, who had suffered from uric acid dyscrasia for some years. The same dosage of Piperazine was adopted as in the preceding case, and with equally satisfactory results.

Dr. von Herget detailed an instructive case in a monograph specially compiled by Dr. Biesenthal mentioned above. The patient, a woman, of 38 years, without any hereditary taint, was attacked by gout during her second pregnancy. The most obvious symptoms were inflammatory processes in the wrists and forearms, which steadily increased after delivery, when the lower extremities were also attacked.

The condition of the sufferer was such that the knee joints were bent almost at right angles, the ankles and wrists much swollen, and

the upper limbs considerably deformed. Pain was very severe during passive movement of the affected parts, and occasionally appeared spontaneously. This condition became more aggravated as time went on, so that the patient was quite helpless and bedridden.

Between February 24th and March 6th, 1892, Dr. Herget prescribed a pint of Gout Water daily, to be taken in four portions. The beneficial effects were observed in two or three days; pain—acutely felt on the slightest movement—sensibly diminished, and in consequence more movement in the joints became possible, and the patient felt generally better.

The influence of Piperazine also showed itself in increased excretion of urine, the quantity rising from 24—35 ozs. during 24 hours to 42—48 ozs., while, at the same time, it had a different appearance in consequence of the larger deposits of urates. The increased elimination of uric acid was also established by analysis which revealed the following results:—

Before treatment	..	0·045 per cent. of uric acid.
On 3rd day of ditto	..	0·054 „ „ „ „
„ 9th „ „	..	0·067 „ „ „ „
„ 10th „ „	..	0·059 „ „ „ „

Further, the solvent action of the Piperazine could be detected in the deposits at the joints, which became less swollen, and the overlying integument loose and wrinkled.

With two intermissions of about two weeks each, when alkaline mineral water was taken, the Piperazine treatment was continued for several months, with steady and continuous improvement both in the general condition of the patient and the amount of uric acid excreted.

Corroborative evidence of the value of Piperazine in arthritis was obtained by Dr. Volmer from a series of unmistakable cases. He prescribed 8—15 grns. daily to be continued for several weeks. The subjective symptoms were relieved in a much shorter time, and no injurious bye-effects were ever observed.

Over 150 cases of gout were treated successfully with Piperazine by Professor Schweninger. From an extensive experience of the treatment of such cases he looks upon the newer remedy as an exceedingly valuable addition to materia medica. Speaking of the local action of Piperazine upon uric acid and concretions in which it occurs, he observes that its solvent effect appears to increase with the circulation in the affected parts, while not only is the uric acid eliminated but secondary inflammatory necrotic changes in the tissues are avoided.

Professor Schweninger administered Piperazine both internally and subcutaneously in doses of 15 to 30 grns. *pro die.* He always obtained good results with the remedy, far superior to those yielded by the ordinary methods of treatment, such as that based on the use of alkalies, of colchicum, and so on; at the same time he never observed any drawbacks in the action of the substance.

After the acute symptoms had subsided, 8—15 grns. of Piperazine were ordered every third day for months afterwards. Subcutaneously 1½ grn. in ten per cent. solution was employed, and in this way large gouty concretions in the elbows, ears, and even eyelids, which otherwise must have demanded surgical interference, were removed by solution.

The injections were made two or three times a day in the neighbourhood of the deposits, while simultaneously 8—30 grns. were given internally *per os.* The author characterised his results as so markedly beneficial that he hoped never again to be without the remedy. Most of the cases which came under his care had been subjected to the principal so-called cures in vain, and yet in these obstinate cases the Piperazine treatment proved successful in 90 to 92 per cent. of the number. Although he had had a wide experience of many acute and chronic cases of gout during a number of years, and had tried all the different remedies, none had given such satisfactory results as Piperazine.

Dr. J. O. Ungerhausen, writing from South Africa, stated that he had used the Piperazine gout water in a few cases with unexpected success; he looked upon it as a remedy worth more than any which had been previously recommended for the same purpose.

III.—IN SOME OTHER ALLIED DISEASES.

The reader will have noticed from the outlines of cases described in the preceding sections that one effect of the administration of Piperazine is an increased secretion of urine. This diuretic action of the base is specially emphasised by Dr. Umpfenbach, who made use of it in a variety of diseases where more active uropoesis was indicated.

In a case of *asthma* in a paranoic patient, who also suffered from fatty degeneration of the heart, with occasional exudation, dropsy, oedema, etc., as well as oliguria and albuminaria, about ¾ of a grn. of Piperazine subcutaneously afforded great relief. He breathed more freely and slept well. The volume of urine increased from 16—18 ounces in the twenty-four hours to 66—70 ounces, while the albuminaria fell off at the same time from 7—8½ to ½ per cent.

As the amount of albumen rose again, and that of the urine diminished, when the remedy was discontinued, it was held proven that these effects were due to the Piperazine.

A similar increase in the volume of urine, with consequent reduction of exudation, was produced in a case of severe *oedematous swelling and infiltration* of the leg, following on fracture, in an old man; confirmatory evidence of the diuretic activity of the preparation was also obtained in other cases, including one of chronic nephritis.

OTHER SEQUELÆ OF THE URIC ACID DIATHESIS. Besides the renal and vesical calculi, the gouty deposits and other symptoms of the uric acid habit already referred to, there are some other affections associated with the presence of uric acid in the blood, in which Piperazine either has been used or would appear to be indicated.

Early in the literature of the remedy, Dr. Krakauer reported (*Aerztl. Central. Anz.*, p. 543), on its use in two cases, which did not belong to the regular forms of gout, and where he obtained results characterised as very satisfactory.

Dr. William S. Disbrow, Newark, N.J. (*Notes on New Remedies*, 1892) expressed his experience with Piperazine as follows: "I have had

opportunity to employ Piperazine, and have noted successful results. Not the least satisfactory effect of the remedy is the relief it affords in *pruritus*. "Who is there among general practitioners who has not seen the muddy-complexioned, dry-skinned itcher,—the unfortunate whose urinary excretion is filled with urates, and whose system is poisoned with the toxic elements due to imperfect nitrogenous elimination? Why do gouty or rheumatic patients complain of this same symptom? You ask them where they itch. They show you, and you find no evidence of local irritation—they simply itch. In these cases I have used the new synthetic remedy, Piperazine, with very satisfactory results, in conjunction with diminished nitrogenous food and hydrochloric acid. The patient's itch may, of course, be due to various causes; but I think I have clearly indicated one cause, and one remedy with which I have achieved good results."

There are, besides those above-mentioned, other forms of disease which are associated with the uric acid diathesis, or in which uric acid is regularly present in the blood, or excreted in abnormal proportions. In these affections a course of the Piperazine treatment is also considered indicated.

In *leucæmia*, for instance, in which an absolute increase of uric acid has been observed by Fleischer and Penzoldt, and a relative increase compared with the amount of urea eliminated, Professor Mosler reported that Piperazine exerted a very favourable influence on the course of the disease.

An interesting series of experiments were also carried out by Bartels with the remedy in *chlorosis*, and its use has been suggested by other authors in *croupous pneumonia*, in which there is a constant increase of uric acid, in *pulmonary emphysema* and in advanced *cardiac degeneration* with oedema.

A review of the entire literature of Piperazine, of which a *resumé* necessarily brief has been given in the preceding pages, throws into

prominence the following salient features in the properties and uses of the base:—

1. Piperazine is non-toxic, however administered.
2. Piperazine passes through the organism without undergoing decomposition, appearing as a salt (urate of Piperazine) in the excretions.
3. When administered in the treatment of the uric acid diathesis Piperazine arrives at the seat of the disease in a form (as carbonate) which readily combines with uric acid (of gouty deposits, etc.), the resultant compound being stable, and excreted, as such, from the organism.
4. Piperazine has a greater power of dissolving uric acid, and the compound formed is much more stable than is the case with any substance yet employed for the same purpose.
5. In the treatment of calculi of the urinary tract, Piperazine has the further advantage over the older agents employed, of being able to dissolve the albumenoid substances which form the foundation of the calculi, holding the earthy constituents together.
6. Being free from caustic or irritant action on the mucous membrane, Piperazine may be injected in solution (2—5 per cent.) into the bladder for the relief of gravel and stone.
7. Piperazine acts beneficially not only in the more characteristic and well-marked forms of uric acid dyscrasia, but also in the remoter, secondary and sympathetic phenomena frequently observed.
8. By its adaptability for local application, both as an irrigation and as a subcutaneous injection, Piperazine has effected excellent results in the treatment of cases of calculi and of gouty tophi which otherwise would have necessitated surgical interference.
9. Piperazine is worthy of trial in all affections which are accompanied by the presence in the blood or the excretions of an excess of uric acid.

METHODS OF ADMINISTRATION AND APPLICATION.

It will have become clear from a consideration of the foregoing that an essential factor in the usefulness of Piperazine is that it should be absorbed as promptly and completely as possible into the blood, and circulate with it through all the tissues, being finally excreted with the urine, carrying with it in firm combination the uric acid, which is the abnormal body to be got rid of.

For these reasons it is advisable, and even necessary, to administer Piperazine in the form of solution, and not as pills and other less-soluble preparations. Other considerations which would lead to the selection of the solution as the most suitable, are the hygroscopicity of the compound and the readiness with which it is taken up by water.

An agreeable mode of taking Piperazine is in some simple aërated water either by itself or in combination with an equal dose of Phenocoll (*v.* p. 43). This plan has also the advantage of securing the administration of the remedy in a sufficiently dilute form. It is a well-recognised and familiar fact that the proportion of water in which a soluble compound is taken is often an important factor in determining the effectiveness of its action.

It may be repeated here, though already stated in the preceding sections, that the routine dosage of Piperazine *per os* is 15 grns. *pro die*, in divided portions; this quantity may, of course, not only be increased in severe and obstinate cases, but also may be reduced with advantage when the more urgent symptoms of a case have been successfully removed and the continuance of the remedy is necessary only to complete the cure or ensure the avoidance of a relapse.

But Piperazine has also been administered with conspicuous success by subcutaneous injection. It was used in this way—dose 1—5 grns.—as a diuretic by Dr. Umpfenbach (*v.* p. 23), by Dr. Bardet against gout (*v.* p. 19), and by Dr. Schweninger in the local treatment of gout

concretions, which otherwise would have called for surgical operation (*v.* p. 23).

The ready solubility of Piperazine in water renders its administration in this way very convenient and simple; solutions varying in strength from 2—10 or even 20 per cent. have been employed, and although not quite painless yet the local tenderness soon passes off when the diluter solutions are employed. In the treatment of general gout the injections were made in the nates, but as a matter of course when the resolution of well-defined concretions was aimed at, the injection was made at the seat of the disease.

Finally Piperazine was applied in solution as a compress, a Priessnitz bandage being saturated with a lotion made as follows:—

R. Piperazine pur.... ... ... grns. xv.—xxx.
Spiritus ... ... ʒss.
Aquæ ... ... ʒiiss.
M. ft. Solutio.

Drs. Biesenthal and Schmidt report that this application had a beneficial effect on gouty swellings, and formed a useful adjunct to the internal treatment.

The prescription of Piperazine with Phenocoll—a specially efficient combination—is separately treated in a chapter following the treatise on Phenocoll (*v.* p. 43).

PHENOCOLL.

Of the various classes of remedies with which synthetical chemistry has enriched our materia medica, none perhaps has assumed much larger dimensions than that of antipyretics. The chief reason for this, if one at all be sought, would probably be found in the fact that the modern development of synthesis, as applied to the production of medicaments, had its origin in attempts to build up in the laboratory a substitute for the natural antifebrile alkaloid of cinchona.

In spite, however, of this multiplicity of antipyretics, it must be added that they have not all succeeded in doing as much as they were expected to, while not a few have proved, when carefully tested, to possess serious drawbacks, such as a poisonous action upon the blood, a tendency to bring about cyanosis, collapse, &c.

Further, the greater number of synthetical antipyretics are comparatively insoluble in water, or only slightly taken up by that solvent. This lack of solubility in water is of course accompanied by a corresponding slowness of absorption, so that the effect is likely to be diffuse and unreliable. It is of course quite unnecessary to emphasise the significance of this difficult assimilation in the treatment of severe febrile temperatures.

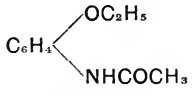
The following pages, containing a brief *resumé* of the literature of Phenocoll, show that it is entitled to take a high rank among the members of the class Antipyretica, by virtue of a number of well-marked distinctive properties.

CHEMICAL NATURE AND PROPERTIES.

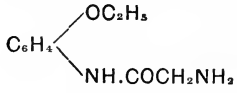
The researches of a number of physiologists and chemists have shown that by the introduction of acid groups into the molecules of acetanilide and phenacetine, compounds are produced which, whatever other properties they may display, do not possess any antipyretic virtues. A good

deal of work was carried out in the investigation of this question which started with the observation of Ehrlich that the affinity which certain substances had for the central nervous system disappeared when one or more acid sulphone groups was introduced into the molecule.

This difficulty was solved in the case of Phenocoll by the addition to the phenetidine group, not of an acid, but of a basic group—namely, glycocoll. The relation of phenacetine and Phenocoll is understood at once by a glance at the following formulæ :—



Phenacetine.



Phenocoll.

Owing to the presence of the amide group (NH_2) in Phenocoll, it is capable of uniting with acids to form salts, of which the hydrochloride has been chiefly used in medicine.

Phenocoll hydrochloride occurs in the form of a white microcrystalline powder, soluble at 17° C., in about 16 parts of water, forming a neutral solution. When crystallised from hot water, it assumes a cubical form, while from alcohol, in which it is soluble only at a fairly high temperature, it separates in the form of needles.

The pure base, Phenocoll, is thrown out of combination in the salt on the addition of ammonia or the fixed alkalies (or their carbonates) to the solution. It forms white matted needles which melt at 95° C., and contain one molecule of water of crystallisation.

The most noteworthy of these physical characters is the ready solubility of the compound in water. This property distinguishes it very markedly from phenacetine, which is chemically closely allied to it, but is only sparingly soluble in water.

PHYSIOLOGICAL PROPERTIES.

Prof. R. Kobert, in Dorpat, was the first to examine the physiological properties of Phenocoll hydrochloride, and from the results of his investigation concluded that it was not poisonous to animals, and that it had no effect even on the blood. In this respect the new

compound contrasted with the majority of synthetical antipyretics previously used.

Experiments on rabbits and other animals with Phenocoll hydrochloride were also made by Professor v. Mering, who found that 1½ grammes (about 24 grns.) could be taken by a large rabbit without any perceptible effect being produced.

Dr. Isaac Ott, Easton, Pa., also made a series of experiments with the compound, and recorded that in frogs it manifested an influence upon the cerebro-spinal axis, evidenced by a general paralysing effect. In rabbits it produced a cyanotic condition of the ears, while the force and frequency of the heart's action was reduced. Even when given in very large doses, the compound does not kill by its effect upon the blood or the heart, but through the centre of respiration. It showed a tendency to diminish vascular tension, while upon the temperature its effect was one of reduction.

These experiments, concluded the author, explained the utility of the compound in rheumatic pains and in pyrexia. It was evidently a drug of considerable power and rapid in its action. This drug seemed to be worthy of a fair trial at the hands of the profession.

An elaborate and exhaustive research into the physiological action of Phenocoll was carried out by David Cerna, M.D., Ph.D., and William S. Carter, M.D., of the Pennsylvania University. They worked at the same time with other synthetical antipyretics, but, as will be seen below, their conclusions were decidedly in favour of Phenocoll.

They pointed out early in the treatise (*Notes on New Remedies*, 1892, September), that unless given in enormous amounts the action of Phenocoll upon the circulation was not marked. At the same time they expressed the belief that, in ordinary medicinal quantities, the substance exerts a slight stimulant effect upon the circulatory system.

In the dogs used for the experiments the blood-pressure fell slightly after the injections, but soon rose again to the normal level. Respiration became somewhat shallow and diminished in frequency, and respiratory failure was the cause of death when the administration was pushed to that extent. These results, it will be noted, agree with those obtained by Dr. Ott.

The authors corroborate the finding of Professor Kobert that no change could be detected in the character of the blood.

Long series of experiments were made upon the action of Phenocoll in reducing the body-heat, both upon normal animals and those in which fever had been artificially produced by repeated small injections (five drops) of putrid blood. In this way a steady fever was brought about, while single large doses of the decomposed liquid were followed by intense febrile reaction, which soon reached its maximum and again fell.

In order to throw light upon the precise manner in which Phenocoll acted as an antipyretic, the normal heat production and dissipation were carefully ascertained first. Then the compound was given and these factors observed again.

Neglecting slight variations as being possibly due to accidental causes or to the conditions of the experiment, the authors noted that fever was brought about the first day by an increase of heat production; dissipation was scarcely disturbed. After the fever was established, the former factor fell, but, being still in excess of the dissipation, the temperature continued to rise.

In common with most synthetical antipyretics, Phenocoll did not exhibit any effect upon the normal temperature. In the case of those animals in which fever had been artificially produced, a decided antipyretic effect was noted. Summing up the results of the two series of experiments carried out upon the circulatory, and the heat phenomena observed with Phenocoll, the authors expressed the following opinions:—

1. Phenocoll, in ordinary amounts, has practically no effect upon the circulation.
2. Large doses diminish the blood-pressure by influencing the heart.
3. Phenocoll reduces the pulse-rate by stimulating the cardio-inhibitory centres. It then increases the rapidity of the pulse by paralysing said centres. The final diminution is of cardiac origin.
4. Upon the blood itself Phenocoll has no action.

5. Phenocoll causes in fever a very decided fall in temperature, which occurs the first hour after the administration of the drug by the stomach. This reduction is the result of an enormous diminution of heat production, without any alteration of heat dissipation.

Drs. Cerna and Carter believe, judging from the results of their work, that of the compounds they examined, the safest for practical purposes, especially as regarded an action upon abnormal temperatures, would be Phenocoll. In their opinion, its advantages are that it is readily soluble, rapidly absorbed and undoubtedly promptly eliminated. They found that it had a very decided power of reducing abnormally high temperatures, and this in therapeutic doses without depressing the circulatory system.

Phenocoll was therefore concluded to be superior as an antipyretic to the other members of the same class investigated.

MEDICINAL PROPERTIES AND USES.

Phenocoll has been successfully employed in at least three principal *rôles* which may be advantageously considered separately. Its primary use of course was as an agent for combating the high temperature of fevers, and its activity in this field will therefore naturally be dealt with first.

I.—AS AN ANTIPYRETIC.

The physiologist von Mering, who examined the effect of Phenocoll in the animal organism under normal conditions, also tried the substance in cases of pneumonia and typhus with the most satisfactory results. He recorded that in doses of one gramme it lowered the febrile temperature about 2° C.; no cyanosis nor collapse was observed.

Dr. Hertel was one of the earliest to publish detailed results obtained with Phenocoll. He employed it as an antifebrile in advanced pulmonary tuberculosis and stated (*Deutsche med. Wochenschr.*, 1891, No. 15) that during the whole time of the application there

were no disturbances of any kind in the functions of the heart, lungs or digestive organs. It was possible by judicious dosage to produce in some cases almost complete apyrexia; he thought, however, that the effect upon the high evening temperature was more marked and reliable than that upon the high diurnal temperature.

Reascension of the supernormal body-temperature occurred without any unpleasant subjective symptoms, such as, for instance, shivering or perspiration.

The author added some comments on changes which occurred in the urine during administration of Phenocoll. It always had a marked dark brownish-red colour, which deepened on long exposure to air. The presence of indican and hydrobilirubin could be always detected. The colour also became more intense with solution of sesquichloride of iron; it was partly cleared away by concentrated sulphuric acid, but never entirely vanished. Viewed by transmitted light, it revealed a peculiar green shade.

Experiments made on various types of fever by Dr. O. Jacobi, showed that Phenocoll was specially effective in the treatment of that characterised as hectic. In doses of 15 grns., it reduced the temperature in 2½ hours to the extent of 1·4° C. This effect was not attended by any unpleasant subjective symptoms.

A lengthy communication by Dr. Benno Herzog to the Giessen Medical Society, contained the record of 11 cases in which Phenocoll was administered as an antifebrile. These included four cases of phthisis, two of erysipelas, and one each of apical pulmonary infiltration, pleuritic exudation, pneumonia crouposa, abscess and febrile cholelithiasis.

The remedy was given in doses of eight grns. at 9, 10, 11 a.m., and 12 noon, then 15 grns. at noon. On a subsequent occasion, the dosage was altered to 4—8 grns. subcutaneously, while $\frac{1}{100}$–$\frac{1}{60}$ grn. of atropine was given internally; by this method the temperature could be kept sufficiently reduced without any outbreak of perspiration. The pulse improved in frequency and general character, and the patients felt well. There was no shivering when the temperature rose again to a febrile level.

In the case of apical pulmonary infiltration, 32 grns. of Phenocoll in four portions were given at first, but subsequently it was found that 15 grns. brought about a state of freedom from fever with little or no sweating or rigors. In the other cases the same dosage—sometimes varied by the subcutaneous administration of eight grns.—was followed by equally beneficial results. In one of the cases of erysipelas, fever permanently disappeared on the third day after three 15-grn. doses.

The conclusions of the author as to the value of Phenocoll in combating fever were expressed as under:—

1. Phenocoll has no unpleasant effect upon the digestive tract. The saline taste may be covered by administration in wafer.
2. In one emaciated consumptive, symptoms of dyspnœa, cyanosis and heart-weakness were observed after 32 grns., but otherwise even much larger doses *never* produced similar symptoms. On the contrary, the patients were gratified with the general feeling of well-being induced, while the respiration and pulse improved both in frequency and character.
3. The antifebrile action, though lacking after small doses, was almost always evident after larger. Phenocoll appeared to work best if given when the fever was at its height. Its action was manifested as a rule in an hour, the minimum temperature was reached in three to five hours, and the febrile level again attained only after seven hours or (rarely) more.
4. Reduction of temperature was almost always accompanied by perspiration, which, however, only reached a high degree in patients with whom this symptom was present otherwise. Further it could be controlled by the simultaneous administration of $\frac{1}{100}$ – $\frac{1}{60}$ grn. of atropine.

A most copious combination of reports upon the use of Phenocoll in malaria was presented by Professor P. Albertoni to the Medical

Society of Bologna. Dr. Prati, who carried out a portion of the work, gave details of twenty-two cases, and concluded that Phenocoll was equal if not superior to quinine in therapeutical activity against malaria, and said he had arrested by its means febrile attacks against which quinine proved ineffective. In those isolated cases where no effect was observed, the author believed that either the dosage was too small, or the absence of effect was a matter of idiosyncracy.

He found that Phenocoll was well borne, doses of 30 grns., at intervals of two hours, not being once followed by disturbance. The taste was easily covered by sugar, and hence Phenocoll was superior to quinine in the treatment of children.

Drs. Alfred Novie and Victor Venturini also reported upon eleven cases, and expressed very favourable opinions as to the value of Phenocoll in malarial fever. Out of the entire number of cases which were treated by the Italian medical men, a cure was effected in 70 per cent., while the result was negative in 15 per cent., and doubtful in as many more. Like quinine, Phenocoll must be given a few days after the attacks have ceased, in order to avoid relapse.

Five cases which illustrated the antipyretic virtue of Phenocoll, were recorded by Dr. Paul Cohnheim (*Therap. Monatsh.*, 1892, No. 1), who used the substance in the in-patient ward of the Jewish Hospital, Berlin. The cases included two of ileo-typhus and three of phthisis. In the former, eight-grn. doses were given, with the result of bringing about a fall of temperature amounting, in some instances, to 2·3°—2·8° C.

In the cases of phthisis, the same doses were given, and the bodily temperature kept within the limits of 37° and 39·7° C. In the second case the patient often had spontaneous falls in the temperature, after the use of the remedy had been discontinued. The pulse, which had been dicrotic for weeks, was hardly at all affected by the medication.

In no case were unpleasant bye-effects, such as collapse, prostration, sickness, tinnitus, etc., observed. The small doses adopted had no appreciable influence on the urine. Pointing out that the results corroborated those of Hertel and Herzog, Dr. Cohnheim urged that Phenocoll is indicated as an antifebrile in fevers, especially of the hectic type.

Dr. Balzer studied the antipyretic action of Phenocoll in 15 cases of various nature, namely, seven of abdominal typhus, four of advanced phthisis, three of pneumonia, and one of erysipelas.

In all the cases of typhus, Phenocoll exerted a very favourable influence upon the course of the fever, and after a few doses there was a decided tendency for the temperature to remain low. A dose of 15 grns. sufficed to reduce and maintain the temperature at a normal level for four to six hours even in the height of the fever.

Similar favourable results followed the administration of Phenocoll in the cases of phthisis accompanied by intermittent hectic fever; when given in the morning the evening rise of temperature was delayed for several hours. Corresponding to the antifebrile action, a slowing of the pulse was generally observed, though this did not occur in the same ratio. The remedy was always administered in capsules as powder, and nausea was never produced.

In a case of erysipelas, Phenocoll was administered in the form of a suppository, and although maintained in position only half-an-hour, an antipyretic effect was produced, indicating that the absorption of the compound from the intestines takes place very rapidly.

Phenocoll proved, in the hands of Dr. Rudolph Bum, a strong and very reliable antipyretic in cases of phthisis, whilst in low fevers it also exerted a beneficial influence. The maximum dosage adopted was 75 grns.

II.—AS AN ANTIRHEUMATIC.

Four cases of rheumatism figured among those described by Dr. Hertel early in the history of the use of Phenocoll. In the first of these, the joints of the right knee, the hip, elbow, hand and fingers, were attacked, as well as the lower portion of the spinal column. All the joints were highly swollen so that active movement was scarcely possible. Antipyrine with morphine, sodium salicylate and acetanilide having been given in vain, Phenocoll was prescribed in daily doses of 75 grns.

On the second day of the treatment considerable improvement was noted, with less swelling of the joints. Painfulness persisted in the cervical vertebræ, but on the whole was so far reduced that active movement of the body could be effected without particular difficulty. By the evening of the fourth day every joint was painless and swelling had passed off.

For about a fortnight after this, the stock of Phenocoll being exhausted, other remedies were resorted to, but pains reappeared in various joints. Finally Phenocoll was again returned to, and the symptoms permanently removed.

In the remaining cases, described by Dr. Hertel, the older remedies were first administered without satisfactory results. Phenocoll in daily doses of 45—75 grns. in separate portions of 15 grns. brought about the cessation of joint-pain in two or three days.

Drawing general conclusions from his cases, the author stated that in severe acute febrile articular rheumatism, partly with complications, the remedy, in daily doses of 75 grns. had a good effect upon the painful joint affections, but none immediately upon the temperature; the latter receded to the normal level only when the other symptoms improved. These beneficial results were obtained after the ordinary remedies had failed.

In a single case of chronic rheumatism of the left hip-joint, Dr. Herzog made two subcutaneous injection of four grns. of Phenocoll into the gluteal region. The diminution of pain was sufficiently marked to enable the patient, who had previously gone on crutches, to walk unaided, though, of course, with considerable difficulty.

Opportunity of observing the antirheumatic action of Phenocoll was afforded Dr. Cohnheim by three cases, in two of which very striking results were obtained. In both the disease was in the acute stage; one patient suffered with marked swelling and pains in the right wrist and hand, while in the other the left knee was the seat of the affection.

In the first case, after a single day of the treatment, free movement of the affected joint was possible, and on the fourth day the patient was entirely free from pain. In the second, pain was entirely got rid of after 11 days of the treatment, but two days later there was a

recurrence; 15-grn. doses were again resorted to and followed by an almost immediate disappearance of pain, and the joints could be freely moved without discomfort. Beyond copious perspiration and consequent thirst, no unpleasant effects were noted, even when 1½ drms. were being taken daily.

The value of Phenocoll in rheumatic affections was most marked, according to Dr. Balzer, in acute polyarthritis, and was particularly useful in cases where salicylates were contra-indicated or did not produce the desired effect. The action of the remedy was examined in six cases of acute and two of chronic polyarthritis, and although (like all antirheumatics) less active in the chronic forms, it produced prompt relief in acute cases where the routine methods of treatment had failed. Like most observers, Dr. Balzer noted that in rheumatic affections larger doses were necessary than when employed as an antifebrile.

III.—AS AN ANTINEURALGIC.

Two instructive cases illustrative of the value of Phenocoll in the treatment of neuralgic pains were recorded by Dr. Herzog. One patient (a woman) suffered from otitis media with very violent headache of the left side, which had only been relieved for a short time by acetanilide. Phenocoll was prescribed in doses of four grns. with the result that an hour later pain was annulled for an hour. On the next day four grns. was given again and the headache disappeared for two hours.

The second case was also of otitis media with very violent pains on the left side of the head; four grns. of Phenocoll dispersed the pain in about two hours. On the three succeeding days the same dose was repeated, being given once in the morning, once in the evening, and the third day, an hour past noon. Then eight grns. was ordered, with the result of effecting in each instance cessation of pain, followed after varying periods by recurrence.

In two cases of sciatica of the right side, subcutaneous injections were made once or twice daily (dose 4—8 grns.) at the seat of the disease. Pain was removed in both instances, though sometimes it set in again in the night.

Dr. H. Aronson, who made a chemico-pharmacological study of Phenocoll and allied compounds, said at the conclusion of the article in which his work was recorded, "As an antineuralgic it displayed, in a few cases observed by me, a safe and prompt action."

Phenocoll was prescribed by Dr. Paul Cohnheim in neuralgias of various parts associated with phthisis, neurasthenia, chorea, enteritis acuta, hysteria and myelitis transversa. The remedy produced the desired effect in all the cases save in the first and last two forms, where also other usual remedies were without beneficial influence. The author observed that after these trials Phenocoll was justly entitled to a place among the recognised antineuralgic remedies. There were no unpleasant bye-effects. Whilst small single doses were ineffectual, the results of eight grns. three times a day were unmistakable.

The influenza epidemics offered a good field for testing the power of Phenocoll over pain of nervous origin, and the literature relating to its employment in these cases showed that it came well out of the trial. Seven cases classed by Dr. Cohnheim under neuralgias were due to influenza, and in these Phenocoll was given with success; pain was alleviated and sound sleep induced. In a few instances variations were observed in the manner in which the pains of influenza were affected; generally those in the back were relieved at once, while the headache was only little or not at all affected. In all the cases, it should be noted, the febrile stage had been passed before Phenocoll was given against the pain.

The fact that influenza was liable to influence the heart and the digestive organs, contra-indicated the use of a number of the ordinary antipyretic and antirheumatic remedies. For the same reason Phenocoll was expected, upon *a priori* grounds, to prove a harmless and efficient remedy in influenza, and the results of the practical trials made with it showed this expectation to be perfectly well founded.

Dr. Lazarus reported on the employment of Phenocoll against influenza, to the Berlin Society, for internal medicine. He prescribed it not purely as an analgesic, but also as an antipyretic and antirheumatic. In doses of eight grns., very satisfactory results were obtained, without any unpleasant bye- or after-effects.

Dr. C. W. Brandenburg, Brooklyn, New York, also treated a number of cases of "la grippe" with Phenocoll, and recorded one (*Notes on New Remedies*, 1891, Dec.) in which, by its means, an attack which threatened to be of a severe type was successfully aborted. The patient, when first seen, was suffering severely with frontal headache and pains in the cervical and lumbar regions of the spine. Other symptoms were considerable muscular soreness, a general feeling of weakness and malaise, coryza and pain in the left ear. The temperature was 103° F., and the pulse 120.

The author prescribed eight grns. of Phenocoll in water every two hours, until four had been taken, and then one to be taken the following morning. At the latter period, Dr. Brandenburg called on the patient, expecting to find him in bed, but instead of this he was away at business as usual. Shortly after the third powder perspiration became marked, aches and pains disappeared, and sound sleep followed until the morning, when the patient felt well enough to attend to business.

Observations of a similar nature were made by Dr. J. O. Ungerhausen, district surgeon of the Lion's River Division, South Africa. It gave very satisfactory results in the treatment of influenza, and also in the first stage of a common cold, when the mucous membrane of the upper part of the respiratory tract was swollen and inflamed. All stages were remarkably shortened, headache disappearing, and catarrh setting in more rapidly, but not developing into so severe a form.

In the Drasche Clinic, Vienna, Dr. Bum found that as an antineuralgic, Phenocoll had a very marked beneficial influence upon migraine, and unpleasant symptoms were seldom observed.

Similar observations were made by Dr. Balzer in three cases of sciatica, in one of lumbar neuralgia, and two of uræmic cephalalgia. In those of sciatica the favourable effect of the remedy was quite manifest; improvement took place gradually, and was not followed by any relapse if the administration of Phenocoll was continued for a few days. The results were not so satisfactory in the cases of lumbar neuralgia and chronic nephritis, accompanied by uræmic headache. The maximum dose *pro die* was 60 grns., and the largest

quantity taken by any single patient was 1½ ounces. The author expressed the opinion that Phenocoll was specially indicated in the forms of neuralgia arising from chills.

DOSAGE AND METHODS OF USE.

It will not be necessary to deal with the dosage of Phenocoll at great length here, since the subject has been included in the preceding sections where the quantities appropriate in each form of disease were indicated. It will be sufficient to say that the average dose as an antipyretic was 75 grns. *pro die* divided into powders of 15 grns. each; sometimes 45 grns. during the day was found sufficient. The general rule that advanced consumptives require smaller doses of antipyretic remedies than the usual must of course be also adhered to in the case of Phenocoll. Outbreaks of perspiration, when occurring to an uncomfortable extent, may be prevented by the simultaneous administration of atropine in doses of $\frac{1}{100} - \frac{1}{60}$ grn.

In malaria 30 grns. was given with intervals of two hours between the doses.

Against rheumatism and neuralgia, full doses—75 grns. daily in divided portions—must be given in order to ensure satisfactory results.

The compound may be prescribed as powders to be taken in wafers or in simple aqueous solution with some ordinary flavouring agents; the latter form is perhaps the best under usual circumstances, as the absorption of the compound is more certainly ensured.

Hypodermically doses of 4—8 grns. were chiefly employed. Dr. Herzog prepared a glycerine solution made by dissolving 15 grns. of Phenocoll hydrochloride in 30 grns. of glycerine warming to 50°—60°C. This solution was determined chemically to contain exactly four grns. in 16 minims; it had to be warmed before use, as in about an hour it became a compact white mass, similar to paraffin in appearance. By using glycerine as the solvent it is possible to administer an appropriate dose without having to inject too large a volume of liquid.

PHENOCOLL AND PIPERAZINE IN COMBINATION.

The pronounced analgesic properties of Phenocoll, particularly in rheumatic conditions, in conjunction with its perfect harmlessness, suggested the idea of giving it in combination with Piperazine for the treatment of gout. While Piperazine would act as solvent for and facilitate the elimination of uric acid, the Phenocoll would relieve the symptoms of topical inflammation due to localisation of uric acid deposits.

Owing to the established custom of taking aërated mineral waters for the relief of the gouty diathesis, Piperazine was also largely administered in carbonated water, when its value in the treatment of gout became recognised. Hence the next step was naturally to prepare a Phenocoll-Piperazine water, each pint of which should contain a certain definite amount of each remedy. The amount selected was eight grns., so that if two bottles were used daily the quantities of the compounds taken would be considerably less than had been administered for prolonged periods without any kind of disturbance.

The employment of such a preparation was of course so simple and safe that it was felt to be worthy of extended trial. Treatment with such an aërated water could be carried on with but little of the constant claim upon the physician's attention, which is necessary in the case of many remedies, owing to the freedom of both the active ingredients from any corrosive or poisonous action. Again, the rapidity with which the compounds are secreted from the body removed any apprehensions as to the production of unpleasant cumulative effects.

The earliest report upon the action of this combination recorded its value in the treatment of the uric acid diathesis.

(*a*) IN GOUTY AND RHEUMATIC DISEASES.

Dr. Ritter, of Dresden, described a number of cases characterised by chronic gouty enlargements of the joints and various morbid local

changes. The Piperazine and Phenocoll were given in daily doses of 15 grns. in the form of solution in aërated water.

In the first case pain decreased after the treatment had been continued nine days and the swelling of the joints was reduced; the urine was clear and abundant, the colour of the skin improved. After four weeks' treatment the patient could walk again and remained free from pain.

In the second the swelling of the joints decreased after a week; there was evident improvement of the general well-being, the appetite and the colour. The amount of uric acid excreted increased.

Pronounced excretion of urates through the skin was a conspicuous symptom in the third case. After a fortnight, symptoms of swelling and inflammation subsided. The total duration of the treatment was three weeks, the same dosage being adopted as in the former cases.

In a case of hereditary gout, four weeks' treatment produced excellent results. The great toe joint was rapidly reduced in size and pain was markedly alleviated. The urine was clear and abundant, vesical catarrh disappeared and urates increased. There was abundant sticky perspiration, but the general feeling was excellent, and the appetite good.

The Phenocoll and Piperazine combination was also tried by Dr. Herget in gout, with the result that beneficial results were observed in two or three days. The pains occasioned by the slightest movement sensibly diminished, and, in consequence, movements of all the joints became more free and easy, and the patient felt generally better. The appetite did not suffer. During an interval of some days the remedy was discontinued, and an ordinary mineral water given. The pains, however, grew in intensity, and the combined treatment was again resorted to, and followed by lessening pain, freer movements and undisturbed sleep.

It was noticed that the medication had a further favourable influence both on the quantity and character of the urine. The secretion increased in activity, the volume passed during the 24 hours practically doubling; at the same time, owing to the larger amount of urates deposited, the fluid has a different appearance. The effect

upon elimination of uric acid, as determined by chemical experiment, was found to be as follows:—

Before commencement of treatment,		0·045	per cent.	uric acid.	
On the third day of	,,	0·054	,,	,,	,,
,, ,, ninth ,,	,,	0·067	,,	,,	,,
,, ,, tenth ,,	,,	0·059	,,	,,	,,

Locally the solvent action of the combination was evidenced in the reduction of the enlargements due to gouty deposits. So rapidly were these deposits carried away that the skin covering them had not time to adapt itself to the altered form of the parts, but became loose and wrinkled.

(*b*) IN VESICAL AND RENAL STONE.

Among Dr. Ritter's cases was one of a man aged 64, who had been operated on 14 years before for vesical stone. At the time of observation there was evidence of the presence of gravel in the renal pelvis and small stones. The principal symptoms were severe renal colic and vesical catarrh.

The combination was prescribed in daily doses of 30 grns. and the treatment continued for 20 days. The vesical catarrh was first to yield, and the urine became clear and abundant. There was a slight excretion of gravel. The patient felt much better in himself at the end of the course.

(*c*) IN GASTRIC TROUBLES.

It would appear that certain forms of digestive disorder are sequelæ of the rheumatic or gouty habit. Such cases are by no means easy to treat, since they are resistant to the ordinary remedies. Consideration of the etiology of these gastric troubles indicates the administration of specific remedies, and in this way excellent results may be obtained in cases which other methods fail to improve.

An illustration of the truth of this view is afforded by the following case recorded by Dr. Schott, Philadelphia (*Notes on New Remedies*, 1890, July). The patient, a lady of about 60 years, who had previously

suffered much from rheumatism, sought relief from annoying pains, due to irritability of the stomach, which always recurred after meals, no matter how carefully the food was selected. Every kind of food was rejected, and nourishment could be administered only in the form of enemata of peptonised beef.

Dr. Schott ordered Phenocoll and Piperazine in 15-grn. doses of each, *pro die*, dissolved in carbonated water. Pain was relieved in a very short time, and then the vomiting stopped. After taking the combination for about six weeks, the patient seemed to have completely recovered, and felt as well as she had ever done in her life.

Dosage and Prescription.

The minimum dose of the Phenocoll and Piperazine combination is 30 grns. daily, that is, 15 grns. of each. This quantity may be increased up to one drm. of each, *pro die*, if the smaller doses are not efficient, or if the case be exceptionally severe. It has been already shown that neither Phenocoll nor Piperazine has any disturbing influence upon the heart or blood, and that they may be taken for prolonged periods without affecting the vital functions of the body.

The best way to prescribe the combination is to order the dose to be taken in a tumblerful of plain or aërated water. It is necessary to point out that if plain water be selected as the vehicle, a certain amount of turbidity may be produced. This, however, is at once cleared up on the addition of aërated water. The medicament may be taken with meals if desired, but seems to be more effective when taken at frequent intervals between them.

CHLORALAMID.

In earlier times the physician was chiefly dependent upon the opium alkaloids, or upon chloral hydrate, in cases where a narcotic or hypnotic was indicated. But these medicaments could not be safely employed in every instance. The continued administration of opium, for example, is soon followed by habituation on the part of the patients, so that the doses have to be constantly increased; at the same time there is the risk of producing the opium habit. Chloral hydrate, again, is not always free from risk, as regards its action upon the heart, nor from unpleasant after-effects, such as giddiness, depression, an unpleasant taste in the mouth, etc.

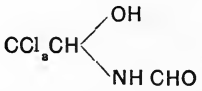
It followed therefore that in the development of synthetical chemistry, as regards the production of medicinal agents, which has taken place of late years, the preparation of hypnotic remedies has excited general interest, and each compound which displayed an action of this kind was exhaustively and searchingly examined.

The advantages of Chloralamid among this class of remedies were, in consequence, early recognised, and all the minute investigations of its properties only served to establish it more firmly in the high position it obtained among pure hypnotics capable of bringing about a sleep indistinguishable in character from physiological slumber.

PHYSICAL AND CHEMICAL CHARACTERS.

Regarded as a chemical compound, Chloralamid is chloral formamide, being an additive product of chloral anhydride CCl_3CHO and formamide $CHO\,NH_2$. One of the hydrogen atoms of the amide group (NH_2) forms hydroxyl (HO) with the oxygen

atom of the chloral, and the resulting compound has the constitution represented by the formula—



It forms colourless lustrous crystals soluble in about 20 parts of cold water and in 1½ parts of 96 per cent. alcohol. It is partially decomposed into chloral hydrate and ammonium formate by water heated above 60° C. (140° F.), but under ordinary conditions, the aqueous solution is quite stable. Alkalies bring about the same dissociation as warm water, but dilute acids have no effect. It melts at 115° C.

Chloralamid has a mild, feebly bitter taste, in no way pungent like chloral.

PHYSIOLOGICAL ACTION.

The first contribution to our knowledge of the effect of Chloralamid upon the healthy animal functions and tissues, was due to Dr. Eugen Kny, of the Strassburg Psychiatric Institute. His work was too lengthy to admit of detailed reference; but generalising, it may be stated that he found Chloralamid a somewhat less powerful hypnotic than chloral, but with the marked advantage of being free from action on the heart, or on the digestive tract; and, further, on account of its comparative tastelessness, much more readily taken. In addition, Chloralamid was not attended by the symptoms of congestion and unpleasant after-effects sometimes observed with chloral hydrate.

The author's experiments, carried out with the view of ascertaining the fate of Chloralamid in the animal organism, showed that chloral hydrate was set free from it; he detected a large proportion of urochloralic acid in the urine of a dog which had been given three drms. of the hypnotic.

The problem had therefore to be solved why Chloralamid, even when exerting its full effect, was without any prejudicial action on the circulatory system, if, as seemed proved, it yielded chloral in the

organism, which had been repeatedly shown, powerfully affected the heart.

Dr. Kny suggested that the difference could be explained from two points of view. In the first place, it might be that the compound was only slowly split up by the free alkali of the circulating blood, so that only small quantities of chloral were set free at any one time. In the second place the depressant tendency of the chloral might be counteracted by the stimulant effect of the formamid, which, like all amide derivatives, had a stimulating action upon the vascular centre in the medulla, and thereby raised the blood-pressure.

Professor A. Langgaard believed that he observed some effect upon the vascular tension, though the heart's action remained vigorous, but the reliability of his experiments was called in question by Professor J. von Mering and N. Zuntz (*Therap. Monatsh.*, 1889) who called attention to the fact that even physiological sleep reduced blood-pressure. Their own elaborate experiments satisfied them that Chloralamid could be safely given, even in cases of disease in which chloral hydrate, on account of its action on the heart and blood-pressure, was contra-indicated.

Concordantly with Kny the authors observed that the effect of chloral hydrate set in more rapidly than that of Chloralamid, but at the same time the hypnotic effect passed off sooner.

Dr. John Gordon, Aberdeen University, having studied the physiological action of Chloralamid, concluded (*Brit. Med. Journ.*, 1891, May 16th,) that, in small doses, it tended to increase the elimination of urea, but that this factor fell off when the doses were large enough to produce a hypnotic effect. The excretion of phosphates was diminished in all doses. No irritation of the gastro-intestinal tract was observed, and no thirst was complained of during its administration.

Dr. H. C. Wood, Professor of Materia Medica and Therapeutics and of diseases of the nervous system in the Pennsylvania University, and Dr. D. Cerna, Assistant in Physiology of the same Institution, carried out a research upon the physiological action of Chloralamid quite recently (*Notes on New Remedies*, 1891, August 15th). Dogs were chiefly used for the experiments, of which some dozen were performed.

in order to ascertain the effect of the compound upon the nervous system, the respiration and circulation. The conclusions arrived at were expressed as follows:—

1. Chloralamid has a slight local action, and in large doses tends to produce mucous diarrhœa.
2. It acts more powerfully upon the cerebral cortex than upon any other portion of the nervous system of voluntary life, thereby causing sleep and muscular relaxation; it is also a feeble spinal depressant.
3. It has a powerful influence in moderate dose upon the respiration, stimulating the respiratory rate by a centric action and probably also increasing the actual amount of air breathed; in toxic doses it causes death by paralysis.
4. Its influence upon the circulation is very feeble, the changes produced by small doses being probably secondary to other effects of the drug; toxic doses, however, depress the arterial pressure by a direct action either upon the heart or upon the muscular coats of the arterials.

The authors inferred from these physiological data that Chloralamid might be safely given in cases of feeble heart; its stimulating influence upon the respiration seemed to render it peculiarly suitable in cases of nervous exhaustion. The observations of Drs. Wood and Cerna throw light also upon the finding of Drs. Hagen and Hüfler, referred to later, that Chloralamid is especially valuable in cardiac asthma.

THERAPEUTICAL EMPLOYMENT.

(*a*) In Insomnia.

As already indicated in the preceding section, Chloralamid may be considered a pure hypnotic without any secondary influence upon the functional activity of the animal organism. Particulars of its action in special cases will be given incidentally in considering the experience of the authors who have employed it clinically, but it will be interesting to present here, at the outset, some general features of its therapeutical effects.

Of course it is impossible to lay down any hard and fast rule as to the time which intervenes between the administration of a dose of Chloralamid and the appearance of its characteristic effects. Many factors, including the mode of administration, personal idiosyncrasy, etc., determine differences in this respect. The average limits may be given, however, as a half to three hours. Out of 55 cases which Lettow observed, with special attention to this point, the action set in after one hour in 29 instances, after two hours in 23, and after three hours three times.

Another interesting feature of the action of the remedy is the duration of the sleep it induces. Broadly considered, the time may vary between two and nine hours. In Lettow's experience—this author made a special study of these details—the sleep lasted from 4—6 hours in 17 cases (out of 21), between 2—4 hours twice, and twice it lasted only two hours.

Dr. Kny, who made the first physiological investigation of Chloralamid referred to above, also tried the compound clinically in 31 cases, prescribing it in doses of 24—60 grns. He found that excellent results were given in psychoses, not accompanied by too active excitement. Regular sleep was also induced in chronic alcoholics and in patients suffering from tabes dorsalis, even when they had been taking large doses of morphine. In four cases of sleeplessness in neurasthenics, satisfactory results were obtained, as also in instances where the morbid condition was due to bodily pain of not too great intensity.

Allusion has been already made to the work of Drs. Hagen and Hüfler on Chloralamid. They believed that it produced a hypnotic effect immediately, that is, by a direct action upon the centres regulating the function. In this respect, however, they differed from Professor Alt, who reached the conclusion that the effect of the remedy was indirectly brought about.

Striking observations were recorded by the two co-workers above-named in cardiac asthma. During the administration of Chloralamid, the pulse rose and the attacks entirely ceased. These effects must be ascribed in all probability to the stimulant effect of the compound upon the respiratory centres.

No less noteworthy were the results obtained by Alt in chorea with Chloralamid. He prescribed 15 grns. three times a day, and in from 5—8 days the affection was almost entirely cured.

Speaking from a considerable experience with Chloralamid, Dr. K. Schaffer pronounced it superior to the other synthetical hypnotics such as chloral hydrate, sulphonal, amylene hydrate, paraldehyde. In 15 cases of progressive dementia paralytica, 30 grns. proved sufficient to relieve the sleeplessness. Where there was slight excitement he gave 1—1¼ drms. or up to 1½ drms. in more pronounced cases. In one instance a morphine injection was simultaneously given. The author specifically mentioned a number of varieties of dementia and delirium in which Chloralamid was successfully given. In general he was satisfied with the action of the compound as an hypnotic, and no unpleasant bye-effects were observed; even after doses of 1—1¼ drms. the patients did not complain of headache, nausea, or other unpleasant symptom. The cases in which good sleep was obtained by means of Chloralamid included one of hysteria and three of hystero-epilepsy.

At a meeting of the Practitioners' Society, New York, Dr. George L. Peabody gave the results of his experience with Chloralamid (*The Medical Record*, 1889, November 16th). Although the effect was characterised as less energetic and prompt than that of chloral hydrate, it proved useful in the most varied forms of sleeplessness, even in alcoholics, and in a case of cerebral hæmorrhage accompanied by great restlessness. It effected great alleviation in two cases of neuralgia with sleeplessness. No disquieting symptoms were ever observed. Chloralamid had the advantages over chloral hydrate of being less irritant to mucous membrane and of having a less unpleasant taste.

Dr. E. Schmidt employed the hypnotic subcutaneously in a case of carcinoma of the rectum. Each ccm. of the solution used contained 0·04 grm. of Chloralamid, and one or two syringefuls were sufficient to induce quiet and refreshing sleep lasting eight hours, in spite of the violent pains suffered by the patients. A similar result was obtained in a case of violent hepatic colic.

Further evidence of the value of Chloralamid was furnished by Dr. Umpfenbach, of the Andernach Lunatic Asylum, who prescribed it in 55 cases (23 men and 32 women). To begin with, 30 grns. of the

remedy were prescribed, increasing up to 1½ drms., *pro dosi* and *pro die*.

In 30 of the cases the desired effect was attained, while in 13 it was only transient, and in 12 absent. The remedy proved most active in hallucinations, paralysis, and the quickly passing excitement-stage of epilepsy, while the less satisfactory results were obtained in the restlessness of imbecility, recent psychoses and melancholia. The sleep lasted a long time, and was unaccompanied by any remarkable symptoms. On the whole, the remedy had no effect upon the gastric functions, but was well borne even when administered for months consecutively. No appreciable influence was observed upon the heart, the vascular or the urogenital system, and collapse-like phenomena were never observed. In a case of tremor essentialis, and another of chorea hereditaria, the motor unrest was considerably reduced under small doses of Chloralamid (8—30 grns. *pro die*).

Dr. G. Genersich, Klausenberg, considered that Chloralamid had established its right to be classed among useful hypnotics, and added that in doses of 45 to 60 grns. the action was reliable and lasting, sleep supervening in from a quarter to one hour after the dose. Secondary symptoms were only unimportant, and the digestive and urinary functions were unaffected. Although the pulse increased in rapidity and became softer, no serious subjective symptoms were experienced by the patients.

Dr. Chas. H. Steele, Professor of Materia Medica and Therapeutics, of the Cooper Medical College, stated (*Pacific Medical Journal*) that Chloralamid was successfully employed in combating insomnia, particularly the simple or idiopathic form not due to excitement or severe pain. It was, furthermore, possible for the wakeful patient to enjoy several nights of natural sleep after a single dose. The best results occurred when the drug was used in insomnia due to nervousness, neurasthenia, hysteria, spinal disease, or old age. When administered in phthisis it was found that the troublesome night sweats disappeared.

Dr. W. Hale White, Guy's Hospital, London, gave Chloralamid in twenty cases of various illnesses in which insomnia was a troublesome symptom. He found (*British Medical Journal*, 1889, p. 1,326) that

the compound produced comfortable sleep in all the patients except two; one of these was suffering from delirium connected with cerebral hæmorrhage, and the other with rheumatic fever complicated by delirium tremens and salicylic poisoning. Some of the other patients were suffering from extremely painful diseases, and yet Chloralamid produced sleep. A woman who had a thoracic aneurysm preferred it to morphine, and another patient who had carcinoma of the stomach also slept better with Chloralamid than with morphine.

Other striking cases were of carcinoma of the liver with intense pain and of cerebral softening; both dozed comfortably after Chloralamid. The sisters and nurses, who saw the patients frequently during the night, told the author that those who took Chloralamid not only slept well and comfortably but better than after any of the hypnotics which had been introduced during the past few years.

In none of the patients did any effects follow that could be looked upon as contra-indications to its use. No depressing results nor headache were observed to be caused by it. Dr. White concluded that in Chloralamid we had a safe hypnotic which did not produce indigestion, and very rarely gave rise to any unpleasant results; the author illustrated his conclusions with brief details of the twenty cases he treated with the hypnotic.

Great care was taken to avoid the disturbing influence of suggestion by Dr. Ed. Reichmann (*Deutsch Med. Wochenschr.*, 1889, No. 31) either by keeping the patients entirely in the dark as to the effects of the medication, or where the patient had become acquainted with the same, by making control experiments with inert substances.

Among the cases detailed by the author were patients suffering from bronchitis and cephalalgia, from chlorosis with mitral insufficiency, from endocarditis aortæ et mitralis, ecstasia ventriculi, renal colic and neuralgia. When 30 grns. of Chloralamid were administered during the day, even if actual sleep did not follow, a feeling of fatigue and sleepiness was induced. More satisfactory results were obtained by doses of 45 grns.; in illustration of this, Reichmann mentions two cases of obstinate insomnia of alcoholism where morphine had hardly any effect, but Chloralamid produced sound sleep.

The question whether Chloralamid could be employed as a hypnotic

with success had therefore, according to Dr. Reichmann, to be answered in the affirmative; and further, he experimentally demonstrated the still more important fact that the remedy had no influence in ½—1-drm. doses upon the circulation. He ventured to say that Chloralamid fulfilled all the requirements of a hypnotic, had a safe, prompt action, and was free from disturbing bye-effects.

Similar conclusions were formed by Professor S. Rabow (*Centralbl. f. Nervenheilkunde*, 1889, No. 15) from experience of the employment of Chloralamid in cases of mental disease. It proved reliable in the large majority of cases of sleeplessness following indulgence in alcohol, as well as in the so-called nervous form of neurasthenia, hysteria, etc.

An exhaustive paper on the value of Chloralamid as a hypnotic was written by Dr. D. R. Paterson (*Lancet*, 1889, Oct. 26th). Observations made on the various vital functions during the use of Chloralamid gave negative results. One patient with simple insomnia was an old woman of 64 who used to spend the night sitting up in bed; 30 grns. of the remedy on consecutive nights, induced, after an interval of 30 to 40 minutes, a tranquil sleep lasting eight and nine hours respectively. When the dose was reduced to 15 grns. the onset of sleep was somewhat more delayed, but it lasted an equal length of time, and was not followed by the slight unpleasant effects which were experienced after the larger dose. An old man of 60, convalescent from an attack of jaundice, and complaining much of resting badly at night, was given 30 grns. on several occasions. Sleep ensued in from 40 to 75 minutes after administration, and lasted eight hours. The slumber was unbroken, very sound, and removed a dull headache from which the patient had been suffering.

Dr. Paterson described other cases—paroxysmal cough, insomnia of phthisis, heart disease, aneurysm of the aorta—in which good results were obtained by administration of Chloralamid. He confirms the opinion of other authors that the hypnotic had no action on the digestive organs; the appetite remained unimpaired.

Dr. George P. Cope made a valuable addition to the literature of Chloralamid in the *Dublin Journal of Med. Science*, 1890, Feb. After describing the cases in which he prescribed the compound, he

expressed the opinion that they demonstrated the hypnotic value of Chloralamid, the sleep brought about lasting five to eight hours, and appearing sound and refreshing. A dose of 25 to 35 grns. was sufficient to cause sleep in patients suffering from melancholia and chronic mania. No recognised evil effects followed the continued use of the remedy for eight days, and only one out of twenty-five persons suffered from gastric disturbance.

According to the observations of Dr. Cope, Chloralamid appeared to be free from the dangers which accompanied the action of chloral hydrate, and in explanation of the distinction, he quoted the words of Dr. D. Leech (*Brit. Med. Journ.*, 1889, Nov. 2nd): "It seems probable that the formamide element, containing as it does a substitute NH_2 group, will stimulate the circulatory and respiratory centres in the medulla, thus tending to counteract the depressing influence of chloral on them."

Dr. Cope corroborated the opinion of Dr. C. Norman, that the chief disadvantages of sulphonal were its bulkiness, insolubility, slowness of action, and high price, and pointed out the Chloralamid formed a contrast in every particular.

Speaking of the indications for the exhibition of Chloralamid, Dr. John Aulde, Philadelphia College, directed attention to the fact that ordinarily large doses did not affect the heart and circulation; in diseased conditions of the system the remedy appeared to be borne with a remarkable degree of tolerance, and after-effects were not objectionable.

Dr. J. M. Thompson, Boston, prescribed about 30 grns. of Chloralamid for a dose, to be taken dry in powder and followed by milk. One patient was a neurotic, subject to sleeplessness, in whom sulphonal produced unpleasant after-effects; 30 grns. of Chloralamid at bedtime brought on sleep in about half-an-hour, which was not followed by any unpleasant after-effects. An habitué of morphine, who had almost entirely discarded the drug, could not get sound sleep; even the use of chloral, bromides and sulphonal was ineffectual. Comfortable sleep was brought on by 30-grn. doses of Chloralamid, lasting four to five hours, and without disagreeable after-symptoms.

Similar satisfactory results were obtained in cases of influenza, followed by delirium tremens, in sleeplessness due to overwork, in angina pectoris, varicose ulcer and alcoholic neuritis. Dr. Thompson said: "I can safely recommend Chloralamid in any case where a hypnotic is indicated, and feel sure that it is the best, safest, and most reliable in use up to date."

Dr. P. Naecke made a number of comparative experiments with Chloralamid, hyoscine and amylene hydrate as hypnotics, which showed that the first-named gave the best results. In his hands it proved free from risk for women suffering from chronic mental diseases, and for epileptics, and did good service not only in nervous agrypnia, but also in cases of excitement. It was best given shortly before the patient's time for sleeping. Though slower in action than chloral, the author thought it might also be more sure, and was confident that it was less dangerous, and that the sleep produced was more refreshing than in the case of chloral.

In three cases put on record by Dr. J. S. Ridge (*Notes on New Remedies*, 1891, No. 8), Chloralamid did even more than was expected of it. The first patient was a consumptive, 60 years of age, to whom, in consequence of insomnia, morphine, bromidia and sulphonal, had been given with only partial success. Chloralamid, in a dose of 30 grns., gave the patient eight hours' sound sleep, without any ill after-effects. This dose always ensured good rest.

In a case of painful vaginal fistula, seven or eight hours' good sound sleep was always induced by 15 grns. of Chloralamid; the patient awoke refreshed.

The third of these cases was one of acute gastritis in an opium habitué. Morphia was prescribed without success; but 45 grns. of Chloralamid was followed by seven hours' sound sleep. Refreshing slumber, free from bad after-effects, was always induced by the same dose of the hypnotic.

Professor M. Charteris, Glasgow University, having administered Chloralamid in many cases of insomnia, where pain was not a chief factor, pronounced it an excellent and safe hypnotic, superior in every way to sulphonal. If it were dispensed in a complete state of solution, it would be found to answer well in cases of sleeplessness.

Comparing Chloralamid with sulphonal, Dr. John Gordon, Aberdeen University, said (*Brit. Med. Journ.*, 1891, May 16th): "It was frequently noticed that, following a dose of sulphonal, the hypnotic action did not take place for a number of hours, so that sleep was projected into the following day, whereas with Chloralamid, sleep, if it supervened at all, came quickly and passed off within six or eight hours. Another claim for Chloralamid over sulphonal is the fact that sleep is more speedy in its onset after administration. The comparatively easy solubility of the substance may so far explain its more rapid action. It was given in doses of 25, 30, 40 and 45 grns."

Nine cases are described in more or less detail by Dr. Gordon, the insomnia against which the hypnotic was given originating in senile changes, heart disease, neurasthenia, phthisis and alcoholism, chronic bronchitis, hysteria and locomotor ataxy, with characteristic "lightning pains." In an old man (84 years) suffering from dilated heart and general anasarca, 20-grn. doses of sulphonal produced what the patient described as "feelings of intoxication," followed by one or two hours of sleep. Thirty grns. of ammonium bromide were without effect, and twenty-five minims of nepenthe gave short uneasy sleep, with dry tongue and headache in the morning. Chloralamid was then resorted to, and a dose of 25 grns. prescribed, with the result that in half-an-hour sleep set in that lasted five hours. On awakening, there was no confusion or headache, but marked refreshment. The same medication was given repeatedly, and continued to act well.

In the case of neurasthenia, the patient stated that on the night succeeding the taking of the powder he slept well, without a further dose. This experience does not stand alone; other observers have recorded cases in which the like phenomenon has been observed.

On the basis of his investigations, both physiological and therapeutical, Dr. Gordon concluded that the results were highly reliable in painless insomnia, and fairly so in insomnia accompanied only by moderate pain. The hypnotic effect followed, as a rule, within half-an-hour of the dose—the sleep induced was tranquil, pleasant and natural—and the awakening free from mental confusion or depression. He further concluded that there was no deferred action, nor was any craving for the remedy excited.

The Therapeutic Committee of the British Medical Association undertook, among other work, the investigation of the value of Chloralamid, and in the report (*Brit. Med. Journ.*, 1890, Aug.), gave details of some half-dozen cases in which the diseases associated with insomnia were cardiac affections, phthisis, neuralgia and acute melancholia. The members of the Committee who recorded the cases were Drs. Charles Angus, William Bullock, and John Gordon, under the direction of Professor T. Cash, F.R.S., Aberdeen.

Save in the case of acute melancholia, doses of 25—40 grns. of Chloralamid produced a refreshing slumber of five to twelve hours duration, and not followed by any bad after-effects. Some of the patients had been previously dosed with opium and other hypnotic remedies without satisfactory results.

Dr. C. R. Hexamer, Stamford, Conn., had among his patients two suffering from alcoholic tremor and insomnia. Doses of 30 to 45 grns. were prescribed with unmistakably beneficial results.

A noteworthy contribution to the literature of Chloralamid was made by Dr. E. Lanphear, Kansas University Medical College, who called attention to its usefulness in quieting the nervous system, and producing sleep after an operation of magnitude. He had convinced himself that it was not always pain which caused restlessness and insomnia in these cases, but the impression made upon the nervous system and on the mind. The usual practice of ordering a morphine injection he considered unjustifiable, and chloral had a dangerous depressing action upon the heart; bromides with hyoscyamus sometimes answered, but most stomachs rebelled against it.

Dr. Lanphear believed that in these cases Chloralamid fulfilled every requirement. It was "the ideal sedative, giving prompt and satisfactory action, reliable results, and absolute freedom from evil-side- or after-effect" (*Notes New Remedies*, 1891, May).

Dr. J. B. Mattison, Brooklyn, had a case of a lady, aged 37, who, when first seen by him, was suffering from weakness, anorexia, depression, and sleeplessness. She had been taking chloral regularly, but this was withdrawn at once and 40 grns. of Chloralamid given. A full night's sleep was obtained without any ill after-effects. Comparative trials with a number of hypnotics showed that Chloralamid

was by far the best—always procuring refreshing slumber lasting several hours.

In the treatment of the insomnia of delirium tremens, Chloralamid proved *the* remedy, par excellence, in the hands of Dr. T. A. Helm. It brought about the quiet and refreshing sleep so desirable, and even essential, to the successful treatment of the malady named.

Among the medical men in various parts of the United States who also emphasised the superiority of Chloralamid to other hypnotics, in the insomnia of nervous and mental diseases, were Drs. J. C. Reeve, J. O. Jenkins, C. R. Phillips, R. M. Brady.

Dr. S. H. Dupon called attention to the value of the hypnotic as a sedative in uterine troubles, especially in aggravated cases with hysterical convulsions. The first dose of 10 grns. frequently gave immediate relief with no return of pain. One of the cases where Chloralamid yielded good results had previously resisted all kinds of remedies.

In the case of an old lady who had suffered from heart disease eight years, and who sought relief from dyspnœa, cough and consequent insomnia, Dr. J. A. Patterson (*Therap. Gazette*, 1891, Aug.) used Chloralamid with great success. He first tried morphine, but this had to be given in such large doses that the author was afraid to continue with it. The synthetical hypnotic in 10-grn. doses, gradually increasing to 40 grns., good rest and sleep in a recumbent posture was obtained. The pulse improved at the same time.

It will be unnecessary to cite all the authors who have found Chloralamid advantageous in insomnia from the most diverse causes. They agreed in praising the readiness with which it lent itself to administration in mixture form and the freedom of its action from unpleasant bye- or after-effects.

(*b*) In Sea-sickness.

Chloralamid, especially in combination with potassium bromide (forming the solution termed "Chlorobrom"), has taken a foremost position among the really serviceable prophylactics against, and cures for, the much dreaded sea-sickness.

One of the chief points in the effect of this compound which has been an important factor in its usefulness in the affection referred to, is, that it is readily retained by the stomach, allaying irritation and arresting nausea. Professor M. Charteris recommended that the remedy should be given after the stage of active vomiting had passed, and stated that at that time it had invariably proved successful, removing all distress, depression, etc., and securing by sleep the gastric and mental repose so urgently required.

Without referring in detail to the reports of the various practitioners who have successfully prescribed the Chloralamid and potassium bromide solution, it may be said that their testimony confirms the experience of Professor Charteris, and shows further that in many cases the complaint may be altogether warded off by taking ordinary precautions to avoid upsetting the digestive organs and resorting to the Chloralamid solution on the appearance of any disturbing symptoms.

A case recently recorded by Dr. Geo. Macdonald, Glasgow (*Brit. Med. Journ.*, 1892, Sept. 17th), is noteworthy, because the patient (a young lady) was suffering from gastric ulcer, which made it the more imperative to check the retching of sea-sickness, owing to the danger of rupturing the stomach. Half an ounce of the solution of Chloralamid (equivalent to 15 grns. of the remedy) was given immediately, and in twenty minutes sound sleep was induced, which lasted for eight hours. With careful subsequent dieting the patient improved steadily during the voyage. The case is a striking illustration both of the safety of Chloralamid and of its reliability in allaying sickness.

METHODS OF ADMINISTRATION.

Among the earliest formulæ given for Chloralamid mixtures were the following:—

℞. Chloralamidi .. .. grns. 45.
Acid hydrochl. dil. .. .. gtt. v.
Syr. Rub. idaei. .. .. ʒss.
Aq. destill. ad. .. .. ʒij.
M. ft. mist. To be taken as a draught.

℞. Chloralamidi .. .. ʒiiss.
Syr. Rub. idaei. .. .. ℥j.
Aq. destill. .. .. ℥iv.
M. ft. mist. Two, three or four tablespoonfuls to be taken before going to rest.

℞. Chloralamidi .. .. grns. 45.
Ac. hydrochl. dil. .. .. gtt. ii.
Spirit vini rect. .. .. m. 15.
Aq. destill. ad. .. .. ℥iij.
M. ft. mist. For an enema.

It is important to remember that although Chloralamid is somewhat slowly soluble in water, heat should never be employed to facilitate solution. Either time must be given for the compound to be taken up in the cold or it must be prescribed with some spirituous preparation in which it can be readily dissolved, and then diluted with water; 20 grns. of Chloralamid dissolves in a drm. of rectified spirit in 15 minutes and then water may be added without throwing the compound out of solution.

Dr. Hale White said a good way of giving the hypnotic was to tell the patient to dissolve it in a little brandy, add water to liking, and drink it shortly before going to bed.

Dr. John Aulde cited the formula given under as convenient and agreeable:—

℞. Chloralamidi .. .. ʒiv.
Spts. frumenti .. .. ℥iij.
Elix. aurantii ad... .. .. ℥iv.
M. Sig. Take one tablespoonful in water every four to six hours, as directed.

Beer and wine have also been used as menstrua for Chloralamid, and spiced wine proved in Dr. Rabow's experience especially agreeable.

Chloralamid should not be given in powder, as, under these circumstances, its absorption may be delayed, and the result consequently less satisfactory. The method adopted by some authors of prescribing the remedy to be taken dry on the tongue, or with milk, is is not therefore to be commended. The desired result *may* be attained in this way, but it is not so certain and reliable, nor so agreeable as when the mixture form is selected.

PARALDEHYDE.

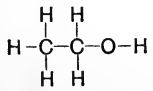
Nearly all the members of the aldehyde group of synthetical remedies possess hypnotic properties, though they exhibit differences in the degree of this effect produced, and also in the character and the prominence of the secondary effects which accompany the primary action.

There is another property which may be characterised as common to the members of the aldehyde group of compounds—namely, a tendency to form condensation products, by virtue of which the molecule becomes more complex, without undergoing any change in the relative proportions of the constituent atoms. That is, the analysis of one of these substances, yields the same figures for the percentage composition as that of the mother substance, possessing a much simpler molecule.

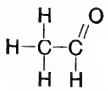
This brings us to the consideration of the

PHYSICAL AND CHEMICAL NATURE

of Paraldehyde. Ordinary ethyl or acetic aldehyde has the formula CH_3CHO, that is, it is alcohol CH_3CH_2OH, from which two atoms of hydrogen have been removed. Graphically, the formulæ of these compounds might be displayed as follows :—



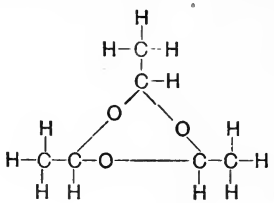
Alcohol.



Aldehyde.

Now, if aldehyde, which is a volatile liquid with a peculiar, somewhat suffocating odour, a sp. gr. of 0·807 at 0° C., and boiling point

at 21° C., be acted upon at ordinary temperatures by polymerising agents, such as acids (HCl, SO_2) and certain salts (especially $ZnCl_2$), it undergoes condensation contracting in volume and evolving heat. The product, Paraldehyde, has a vapour density which corresponds to the formula $C_6H_{12}O_3$, from which it appears that it is formed by the condensation into one molecule of three molecules of aldehyde, the union taking place through the medium of the oxygen atoms in the latter. Its constitution is represented thus :—



The physical and chemical properties of Paraldehyde compared with those of the mother substance—briefly given above—correspond closely with the nature of the change by which it is formed—that is, they are those of a more condensed body.

Paraldehyde, when pure, is a colourless liquid with a sp. gr. of 0·998 at 15° C. and boiling at 124° C. Subjected to a low temperature it solidifies to a crystalline form and melts again at 10·5° C. At 13° C. it dissolves in eight parts of water ; unlike most substances, its solubility is not increased by raising the temperature of the water, on the contrary an aqueous solution saturated at the ordinary temperature becomes turbid when heated, and a large proportion of the dissolved Paraldehyde separates out.

Though fairly stable under normal conditions, Paraldehyde—as the chemist would expect from the mere consideration of its structure—is somewhat easily split up. It is very sensitive to oxidising agents, and is partly reconverted into ordinary aldehyde by mere ebullition ; in the presence of a small quantity of sulphuric acid the change is complete on boiling.

In common with aldehydes generally, Paraldehyde is a powerful reducing agent, forms an aldehyde resin with warm potassium hydrate, and so on.

The Importance of Purity

is generally recognised in the domain of medicine, and it is owing to the spread of this principle that the use of medicinal agents of definite chemical composition has attained such large dimensions of late years. Bodies which have an unvarying chemical composition and well-defined physical characters are more likely to produce reliable and exact effects than preparations of which no two batches are ever exactly similar in composition and therapeutical activity.

But in the case of Paraldehyde it is especially important that the substance used in medicine should be absolutely pure. It has been repeatedly found that specimens described as "Paraldehyd. purum" contained not only ordinary aldehyde, but also amylaldehyde.

Now even only small quantities of these impurities are sufficient to render the Paraldehyde unfit for medicinal use. Ordinary acetaldehyde, as stated above, has a pungent, almost suffocating odour, and amylaldehyde is poisonous to an unmistakable degree.

No doubt it was the consequence of the introduction of specimens containing these impurities into medicine, which prevented the compound in the earlier days from attaining that prominent position among hypnotics which it deserved. Hence the necessity of emphasising the importance of seeing that patients get only such a brand of Paraldehyde as is really absolutely pure, not only in name but in fact.

The physical factors—sp. gr., boiling point, congealing point—mentioned above, are valuable tests of the purity of the compound. The odour, however, is frequently sufficient in itself to indicate the presence of impurities. Pure Paraldehyde has a spicy aromatic odour, and when ʒ j. or ʒ ij. are evaporated gently on a water-bath, no unpleasant smelling residue (higher aldehydes from fousel oil occurring in the spirit from which the preparation was made) should be left.

PHYSIOLOGICAL ACTION.

It seems to have been assumed at first that Paraldehyde would have the same effect upon the animal organism as aldehyde. The careful

work of Dr. Vincenz Cervello, Strassburg Pharmacological Laboratory, showed the unsoundness of this view.

Doses of about ½–¾ drm. produced in rabbits of average size narcosis, lasting six or seven hours, not preceded by any stage of excitement. On awakening, the animals were at first a little unsteady on their legs, but soon regained their normal certainty. No further disturbances were noted; the animals seemed perfectly well, and took food eagerly.

During the stage of profound narcosis the breathing became slower, but the pulsation of the heart, so far as could be estimated by the hand, remained strong. No change was perceptible in the pupils.

The effect upon dogs was similar, quiet sleep being induced without previous excitement. The diminution in the frequency of the respiration was not so considerable as in rabbits. That the compound was absorbed very rapidly was shown by the fact that five minutes after injection the gait of the dogs became unsteady and sleep soon supervened.

Dr. Cervello's conclusions may be summarised as follows:—

1. Paraldehyde acts principally upon the cerebrum and partially upon the medulla oblongata and spinal cord.
2. In large doses it arrests the respiration, but the heart's action continues. The animals could be restored by means of artificial respiration.
3. There is no stage of excitement previous to the narcosis as in the case of ordinary aldehyde, nor any subsequent functional disturbance.

Cervello's researches left unanswered, however, the question whether the preparation had any effect upon the digestive function or not. Our knowledge of this side of the action of Paraldehyde we owe to Dr. John Gordon, Aberdeen University, who carried out a series of experiments, with the view of determining the action of hypnotics on digestion.

Test-tubes were used of equal size and form, containing ½ gramme of stained fibrin, two decigrammes of pepsina porci, two ccs. of two per cent. hydrochloric acid, 15 ccs. of water, with varying quantities of the drugs under examination. One tube without any medicament

was used for control purposes. The set of tubes was placed in an incubator, and kept as near as possible at the normal body heat.

In the case of Paraldehyde, the test-tubes were capped with india-rubber to prevent evaporation. The quantities of the hypnotic added to the tubes were 0·3, 0·75 and 1·25 cc. respectively. The remarkable result obtained was that in nine hours the digestion of the fibrin was complete in the tubes containing the large quantities of Paraldehyde, and well advanced in the third, while, in the control tube, very little progress had been made towards digestion.

From a number of experiments, Dr. Gordon drew the conclusion that the presence of Paraldehyde, even in minute quantities, accelerated the digestion of fibrin, and that the greater the proportion of the hypnotic present, the more rapid the peptonising process.

It was also observed that putrefaction was prevented by the larger proportion of Paraldehyde, and delayed by the smaller.

MEDICINAL PROPERTIES AND USES.

The physiological examination of Paraldehyde outlined above indicated its value as a harmless but efficient hypnotic. Dr. Cervello described a case of sciatica, in which two drms. of Paraldehyde was given as a three per cent. solution in three doses, with half-hourly intervals. Two hours after the last portion was taken, the patient was asleep, and did not awake till ten and a half hours later. No headache, nausea, or other inconvenience was experienced.

Dr. Gugl used Paraldehyde 336 times, and found that in from half-an-hour to three hours it produced calm, deep, and refreshing sleep, closely resembling natural slumber. The duration of the sleep varied from three to seven hours, or even ten hours, according to dosage and individual idiosyncrasy. He obtained evidence that it could be administered without hesitation in cases of heart disease, even when of very pronounced gravity. The conviction forced itself upon Dr. Gugl, that the best results were obtained in constitutional or acquired neuropathic conditions in hysterical and neurasthenic, rather than hypochondriacal cases. The author cites a number of illustrative

cases which also indicate the freedom with which Paraldehyde may be given for prolonged periods without causing disturbances.

Good, and even, in some instances, brilliant results were obtained in cases of alcoholism, and in the simple nocturnal restlessness of dementia paralytica and senilis. When the hypnotic effect was not marked, as was sometimes the case, an evident sedative action was perceptible.

In a case of hystero-neurasthenia, with unusually painful spinal affection, the patient declared that immediately after taking Paraldehyde, she always became sensible of an essential decrease in the pains.

On the whole, the author concluded that Paraldehyde was a powerful hypnotic, preferable in many cases to chloral, on account of its freedom from danger, even when its use was long continued. In mental diseases and neuro-pathology, the physician had gained, in Paraldehyde, a powerful aid in combating sleeplessness.

Similar evidence was afforded by the cases under treatment by Dr. J. Peretti (*Berl. klin. Wochenschr.*, 1883, Oct. 1st); even decrepit and paralytic persons could take the remedy without danger, and heart disease was not a contra-indication to its use. In one case a patient took over six ozs. in forty-two days; and in another, nearly 5½ ozs. was taken in forty-one days, without any injurious effect.

A very trifling fall of temperature was produced, and there was no congestion or alteration of the pupils. The results of Dr. Gordon's investigation of the effects of Paraldehyde on digestion outlined above were clinically antedated by Peretti's observation that not only was the hypnotic free from prejudicial action on the digestion, but some persons were able to record an appreciable beneficial influence upon the digestive function and the appetite. The after taste was not sufficiently marked to give occasion for complaint, or to affect the appetite. Further, even prolonged use did not interfere with the digestive or intestinal functions.

The author expressed the advantages of Paraldehyde over chloral hydrate, as follows:—

1. Even in large doses Paraldehyde is free from dangerous action on the heart.

2. The action of Paraldehyde is not cumulative.
3. Paraldehyde rapidly induces sleep without previous symptoms of excitement or congestion.
4. Patients awakening from the sleep induced by Paraldehyde do not experience any disagreeable sensations.

Prolonged experience convinced Prof. v. Krafft-Ebing that Paraldehyde was an efficient and safe hypnotic if given in suitable doses. He warned medical men, however, against prescribing the compound in doses exceeding the limit of safety. This warning is now less necessary, since it has been found by various authors, and is specially noted by Dr. E. M. Sympson, that Paraldehyde is effective in comparatively small doses. Dr. Sympson obtained good results in delirium and various kinds of insomnia with the remedy.

By Dr. H. Dehio, Paraldehyde was characterised as "the sovereign remedy" among hypnotics. In his experience it produced a sleep frequently lasting seven or eight hours, and extraordinarily like natural slumber; no headache, giddiness, or other symptoms usual after narcotics, were observed. Like the physiological sleep, that produced by Paraldehyde was most profound during the first two hours.

Reference has been already made to the work of Dr. Gordon on some points in the chemico-physiology of Paraldehyde. The author, who is Assistant-Physician of the Aberdeen Sick Children's Hospital, mentions incidentally that he used the compound clinically in a number of cases, but does not give any details.

DOSE AND METHOD OF ADMINISTRATION.

The average dose of Paraldehyde is about a drm., but the limits are given as 45 ms. to 2½ drms.; not more than 1¼ drms. should be given as a single dose, nor should the maximum quantity mentioned above be exceeded during the twenty-four hours.

Owing to the occasional employment of inferior and impure specimens of Paraldehyde, somewhat exaggerated statements were made as to its flavour, and the odour it communicated to the breath of the patients. It appears according to Dr. Dehio and others, that

the pure preparation is generally taken without any complaint or any effect upon the appetite.

Paraldehyde may be conveniently taken with rum, milk or flavouring essences, while aromatic bitters, like the tincture of orange, have been favourite correctives. The tincture has the futher advantage of readily dissolving the remedy. The following formulæ yield agreeable mixtures :—

℞. Paraldehyd. .. .. ʒiij.
Tinct. Aurantii .. .. ʒvj.
Syrupi. simplic. .. .. ʒiij.
M. Sig. One Teaspoonful (15 ms. of Paraldehyde) for a dose.

℞. Paraldehyd. .. ..
Mucilag. Acac. aa. .. .. ʒiv.
Syrup. Amygd. .. .. ʒj.
Aquae ad .. .. ʒvi.
M. ft. Emulsio. Two Tablespoonfuls (40 ms. of Paraldehyde) for a dose.

Paraldehyde is very readily absorbed from the digestive tract, but in some instances it has been administered subcutaneously. Mr. Kéraval employed a solution of 10 ms. each of Paraldehyde and cherry laurel water made up to 40 ms. with distilled water. Before use he immersed the bottle in warm water in order to ensure perfect admixture.

℞. Paraldehyd. .. .. m. lvi.
Spir. Menth. Pip. .. .. m. j.
Olei oliv. q.s. ad .. .. m. cxij.
M. ft. solutio.

The solution prepared according to this formula was preferred by Drs. Langreuter and Strubisch. In any case the method seems to be somewhat painful and, save in very exceptional instances, would not have any advantages over the usual mode of prescribing.

...CALIFORNIA...

CHLORALS AND CHLOROFORM.

CHLORAL HYDRATE was first recommended as a hypnotic and substitute for opium by Dr. O. Liebreich; the mother substance chloral was discovered by Liebig in 1832, having been prepared by him from dry chlorine gas and alcohol.

One of the most important chemical properties of Chloral hydrate, CCl_3COH, H_2O, is its hydrolysis in the presence of alkalies into chloroform and formic acid, thus:—

$$CCl_3COH\ (H_2O) = CHCl_3 + HCOOH.$$

This reaction is practically applied for the preparation of the purest Chloroform (*v. infra*).

In the use of Chloral hydrate as of each member of this group of bodies the greatest care must be taken to ensure perfect purity, as the organic compounds of chlorine are characterised by a powerful physiological action, and aldehydes or oxidation products, as well as free chlorine, either reduce the activity of the preparation or have a marked local irritant effect.

It is quite unnecessary to describe the physiological or therapeutical action of Chloral hydrate in any detail, or to refer to the enormous literature of its employment in medicine. Its chief importance depends upon its hypnotic properties; while it has some disadvantages compared with opium preparations, it has also many advantages and is not rarely efficacious where they fail. The best results are yielded in delirium potatorum, in puerperal mania, enuresis nocturna, convulsive affections (eclampsia, uræmic cramps, epileptiform convulsions in children, tetanus, chorea, etc.).

The unquestionable success of the remedy in gastro-intestinal affections of children depends evidently upon its simultaneously antiseptic and irritant action. The same is also true of most of its external applications.

BUTYL-CHLORAL HYDRATE, which was at first regarded as the chlorine substitution product of croton aldehyde, and therefore termed croton-chloral, must be given in much larger doses than Chloral hydrate, in order to attain the same degree of hypnosis. Comparative experiments with Butyl-chloral and Chloral hydrate showed that the narcosis of the former lasted only a third as long as that of the latter. A peculiarity of the remedy is that it principally produces anæsthesia of the cerebral nerves while it affects those of the body much less. It is therefore especially serviceable in the treatment of trigeminal neuralgia. It has, however, been successfully given in convulsive and irritant cough and the neuralgic pains of tabetic patients.

As a sedative, Butyl-chloral hydrate is given in doses of ½—1 drm., preferably in solution.

CHLORAL-CHLOROFORM. Reference has been already made to Chloral hydrate as a source of Chloroform (*v. supra*) and the equation given illustrative of the process by which it is formed. The product is characterised by its high standard of purity and absence of foreign compounds. It answers satisfactorily to all tests and is appreciably less prone to spontaneous decomposition than the ordinary chloroform of commerce.

Though the presence of oxidation products or foreign chlorinated compounds is prejudicial to the value of all the members of this group of compounds, it is especially so in the case of Chloroform, which is principally used by inhalation. Hence the superiority of a product which is made from a compound of definite chemical character which can be readily obtained in a condition of great purity.

SALOL.

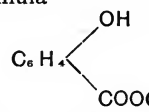
The important *rôle* which phenol played in antiseptic surgery and medicine was only restricted by its poisonousness. When used internally, apart from its local caustic action, it was exceedingly liable to produce symptoms of toxic action, which not only necessitated the observance of great caution in its employment, but further absolutely contra-indicated its use in a considerable number of cases.

At the same time, there is a fairly large group of diseases known to be due to, or at least associated with, the presence of pathogenic micro-organisms in different parts of the intestinal tract. These called for the administration of compounds which, while free from a general poisonous effect upon the organism, would yet be capable of directly attacking *in situ* the bacteria which were keeping up the disease.

The problem was, therefore, to find some combination of phenol which should be free from its poisonous action but possessed of an equal, or, at least, of a marked antiseptic power. Such a compound was discovered in Salol, one of a group of aromatic esters first prepared by Nencki in 1883.

CHEMICAL NATURE AND PROPERTIES.

Salol is systematically termed phenyl salicylate, being represented by the constitutional formula—



It occurs in the form of white powder, seen under the microscope to consist of tabular crystals; or these crystals may be large enough to make it necessary to describe the compound as being in crystalline

tables, which are well defined and transparent. Salol has a feeble aromatic odour, but being practically insoluble in water, has little or no taste.

In alcohol the compound is soluble in the proportion of 1 in 10, while ether takes up rather more than three times its weight. When an alcoholic solution of Salol is poured into water a liquid having the appearance of an emulsion is produced, which really contains the substance suspended in a fine state of division. It is also soluble to a considerable extent in fatty and mineral oils, in turpentine, copaiba balsam and sandal-wood oil. It will be seen below that this solubility of the compound in essential oils and oleo-resins has a practical value in its administration. When subjected to the action of heat, Salol melts at 42°—43° C., and if the temperature be raised (the substance being supported on platinum foil) burns away with a very smoky flame, leaving no residue.

If an alcoholic solution of Salol be added to solution of ferric chloride (perchloride of iron) the only result is the appearance of turbidity; if, however, the process be reversed and the solution of ferric chloride poured into that of the Salol, the characteristic bluish or violet colour of phenol is produced. Bromine water precipitates a monobromo compound that crystallises from alcohol in long needles.

PHYSIOLOGICAL PROPERTIES.

The discoverer of Salol, Professor Nencki, compared it in its physiological relations to the fats; like these it was split up by the pancreatic juice into free acid and an alcoholic group, that is into salicylic acid and phenol. He also believed that the compound passed through the stomach unchanged, because the feeling of malaise which almost invariably follows the administration of sodium salicylate was entirely absent when Salol was given.

A careful research into the destiny of Salol when administered by the mouth was made by Dr. R. Sievers and Professor C. A. Ewald (*Therap. Monatsh.*, 1887, Aug.). In 25 experiments in which the

extracted gastric juice after a dose of the substance was tested every half hour for free salicylic acid, negative results were uniformly obtained.

On the other hand, it was observed that in contact with alkalies, even at the normal temperature, and especially at that of the blood, the compound was split up into its components. Since the pancreatic juice and intestinal fluids are alkaline, it followed that when Salol, having passed through the stomach unchanged, entered the intestines it would be there split up into phenol compounds and salicylic acid.

It was experimentally proved by the authors that every part of the intestinal tract was capable of effecting the dissociation of Salol. They further found that when Salol was brought into direct contact with the intestinal mucous membrane, 20—30 minutes were required before its constituents appeared in the urine. In healthy individuals an hour proved to be the extreme limit of time between the administration of the compound and its appearance in the urine.

About the same time Professor Sahli studied the dissociation of Salol in the organism, and obtained results which corroborated those of Drs. Sievers and Ewald.

In the well-known Pharmacological Institute of Dorpat, under the direction of Professor Kobert, G. Willenz carried out a searching investigation of the conditions under which the substance split up into its components. He found, like the preceding workers, that the members of this class of compounds did not split up in the stomach, but were resolved into their components only by the alkaline juices of the intestines. Owing to their dilatory effects upon the vascular system, the substances exerted an antifebrile effect.

In a research of later date than that mentioned above, Professor Sahli adduced proofs that large doses of Salol could be taken—doses which corresponded to an amount of phenol far exceeding what could be safely given as such—without any symptoms of poisoning. The author expressed the opinion that when given in large doses Salol was possibly absorbed undecomposed, while further it might be that the phenol was very gradually separated from combination and excreted as fast as it was set free, or converted into harmless compounds with sulphuric or glycuronic acid.

Experiments with Salol upon animals were carried out by Dr. Hesselbach, which demonstrated, beyond doubt, that the dosage of the substance should not be based upon that of phenol. It was proved by the fact that the lethal dose of Salol for animals amounted to 7·6 grms. per kilo (about 53 grns. per lb.), corresponding to a dosage of 532 grms. for a man of 70 kilo (154 lbs.) weight.

BACTERIOLOGICAL EXPERIMENTS.

The most elaborate research on the antiseptic action of Salol was conducted by Professor Sahli. The first series of experiments was made on finely-minced pancreas, diluted with water to a pasty consistence, and containing various proportions of Salol. It was found that 2½ per cent. of the compound was sufficient to prevent the process of putrefaction.

It was stated by Koch that the antiseptics were of no value when used in oleaginous solution; under these circumstances they were, according to his investigation, practically inert. Professor Sahli made a special series of experiments, with a view of testing the truth of this general statement in the case of Salol; from these it appeared that even in oleaginous solution, the compound exerted a powerful kolyseptic (or development hindering) action upon bacteria. Apparently even it was more active when dissolved in almond oil than when used in powder—a result ascribed by the author to the more uniform admixture of the antiseptic with the substance containing the bacteria.

It is unnecessary to refer to all the work which has been done in the investigation of the antiseptic activity of Salol. In the following section, dealing with its use in medicine, a good deal of evidence of its power in this direction will be met with.

THERAPEUTICAL USES.

Salol was recommended in the first instance as a substitute for salicylic acid, presumably of more rapid effect, and free from irritant

action upon the stomach, as it was not separated into its components until it had arrived in the duodenum. This view of the medicinal function of the compound determined of course the mode of its employment, and it will be perhaps advantageous to follow, to some extent, in dealing with its various uses in medicine, the chronological order of their development.

(*a*) INTERNALLY.

1. Against Rheumatism.

Salol was employed in 27 cases of typical articular rheumatism by Dr. Bielschowsky, being given in capsules in doses of 1¼ drm. *pro die* within five hours, and in one case, two drms. within eight hours. Smaller doses of 30—45 grns. were given only for the after treatment of some cases where slight pains persisted. Of the 27 cases, 19 were rapidly and completely cured; in two, the effect was only slight, and the remaining six passed into the chronic form.

Relapse was observed only eight times, and in each case was cured by returning to the use of Salol; smaller quantities of the medicament sufficed than in the first attack.

The smallest quantity which sufficed to remove the symptoms amounted to 3½ drms., and, on the average, the treatment had to be continued for from four to eight days before a cure was attained. Once, the disease resisted for ten days, but in several cases every trace of the affection disappeared after three days. In four of the patients, slight disturbances of the cardiac activity appeared, but were no longer in evidence when they were discharged. Three suffered from mitral failure, in consequence of earlier attacks of rheumatism; they were not aggravated by the fresh onset of the disease.

The author concluded, from his cases, that Salol must be regarded as a specific in acute rheumatism, having the advantage over salicylic acid and the other usual remedies of being free from any bye-effects. The most careful observation of the patients satisfied the author that this was so; neither exanthema, perspiration, nor digestive disturbances were seen.

Almost simultaneously, clinical experiments with Salol in rheumatism were carried out by Dr. Siegfried Rosenberg in the Jewish Hospital, Berlin. He reported (*Therap. Monatsh.*, 1887, No. 2) that on the whole, the effect was promptly exhibited; as a rule fever disappeared and the painfulness of the joints was alleviated after twenty-four to forty-eight hours. The longest time which elapsed before symptoms were removed was five days, and in a single case only, and that of very severe nature, was the remedy entirely without effect.

So long as fever and pain persisted in the joints, 1½—2 drms. of Salol were given daily in single doses of 15 grns. at intervals of one or two hours. As soon as the patients were free from fever and pain, the dose was reduced to 1¼, 1 drm., 45 and 30 grns. *pro die* (always in portions of 15 grns. each) in the hope of preventing relapse.

The colour of the urine assumed an olive-green shade, deepening to blackish green. In a few patients it cleared up later in spite of continued use of Salol, and exhibited a greenish coloration only on the upper surface where it came in contact with the air. Unlike the preceding observer, Rosenberg recorded tinnitus as sometimes following the use of Salol, but agreed with him that malaise, eructation and nausea were very rare, and that the persistent digestive disturbances of salicylic acid were never produced. Salol was also superior to salicylic acid in its freedom from any irritant effect upon the mucous membrane of the stomach.

Dr. Herrlich gave Salol in 25 cases of acute rheumatism with satisfactory results. He employed doses of 15 grns. frequently repeated, and recommended this *modus procendi* as preferable to large doses less often.

Concordant results were recorded (*Berl. klin. Wochenschr.*, 1887, No. 9-11) by Dr. F. E. Georgi, who also tried Salol in acute rheumatism. Unpleasant secondary effects were not at all manifested. The average dose adopted was 2½—3 drms., and the writer believed that thorough and lasting effects were attained by continuing the administration of Salol in decreasing doses.

The crucial test of the safety of a remedy is its effect when administered to children, who are most susceptible to the action of medicinal

agents. This test, as regards Salol, was carried out by Professor Demme, of the Jenner Children's Hospital, Berne.

From 45 to 60 grns. of Salol daily, in doses of 15 grns., with intervals of two to three hours, were given to two boys (of 8 and 13 years respectively) so long as fever, swelling and pain persisted. In one case the administration was continued in this way five days and in the other seven days. As the symptoms were alleviated the dose was reduced to 30 grns. and during convalescence to 15 grns. The duration of the attack did not exceed 14 and 16 days in these two cases.

In another instance the patient was a girl of seven years, with fever and severely attacked joints; the afebrile state and reduction of the local swelling were attained in 48 hours, during which 1¼ drm. of Salol was given. Here, as in the cases of the two boys above mentioned, there was no relapse.

Salol had also a favourable influence upon two cases of endocarditis and pericarditis which were of rheumatic origin. Before the specific remedy was given, the abnormal frequency of the heart's action was reduced, and the blood-pressure regulated by the administration of digitalis.

The very markedly unpleasant after-effects of salicylic acid and salicylate of soda induced Dr. Aufrecht to give Salol a trial, with noteworthy results (*Deutsche med. Wochenschr.*, 1888, No. 2). The remedy was given in 30 cases, 1½—2 drms. daily in 15-grn. doses. One patient (a woman) took half a pound of the substance in daily quantities of 1½ drm., and bore the treatment well. Dr. Aufrecht formed the opinion that, in chronic rheumatism, Salol was undoubtedly superior to salicylic acid. In acute cases he gave salicylic acid until the fever was reduced (which required two or three days), and then replaced it by Salol.

Dr. Lepine (*Lyon Médical*, 1886, July) found that Salol was more effective than salicylic acid in relieving the pains of rheumatism. Daily doses of one to two drms. were well tolerated.

Among American observers who have used Salol, Drs. C. J. Sauer, Brooklyn, New York; F. G. Dawnitz, St. Louis, Missouri; and Wile, of Danbury, Connecticut, may be mentioned. They all spoke very highly of Salol as much superior to any of the salicylates, and as a

reliable remedy for gout and rheumatism. Dr. Wile used the compound in rheumatism complicated with Bright's disease; 15 grns. of Salol was prescribed three times a day with a milk diet. The improvement was at once apparent and steadily progressed.

An interesting case of rheumatism, in which Salol was used, was described in a medical journal of Japan, by Dr. J. Kimura. The patient was attacked in both knee-joints, and had been long under various treatments without good effect. At first 10, and later 20-grn. doses of Salol were prescribed. In about three months the pain had entirely disappeared, and the patient, who had been quite unable to walk, could move about very well with the aid of a stick. Previously there had been habitual constipation; but after the use of Salol, the bowels became quite regular.

Thirty cases of articular rheumatism were treated in the Magdeburg Town Hospital, by daily doses of 1½—2 drms. of Salol, under the direction of Dr. Behm. The results were characterised as very satisfactory, and there was a noticeable absence of unpleasant bye-effects. Appetite nearly always remained good, and the amount of perspiration produced was always less than that which accompanied the use of salicylic acid.

2. In Diseases of the Genito-Urinary Tract.

While Dr. Rosenberg was examining the anti-rheumatic virtues of Salol, Dr. L. Feilchenfeld, in the same institution (Jewish Hospital, Berlin), tried it in vesical catarrh and pyelitis. Single doses of 15 grns. two or three times a day, produced good effects in all cases; the urine, when previously alkaline, became acid, its volume increased while the amount of pus excreted decreased.

These favourable effects were especially marked in acute cases, and in cystitis gonorrhoica.

In two cases of pyelitis the pus was unmistakably diminished in amount to an extent not attainable by other means. Even when the case was one of prostatic hypertrophy, the quality of the urine was improved by the use of 45 grns. of Salol.

The dosage employed was not, as a rule, followed by any unpleasant effects. The so-called carboluria was frequent, but soon passed off again, although the remedy was uninterruptedly continued. Gastric troubles were never observed.

Professor Demme (*Ber. d. Jennerschen Kinderspital in Bern* No. 20) recorded beneficial results in two cases of vesical catarrh. In one case the affection was the result of cantharidin-poisoning in a boy of five years. From 20—40 grns. of Salol was prescribed, and on the second day the previously alkaline urine became acid, and the diuresis more abundant and painless; after a fortnight's use of Salol, the boy could be looked upon as cured. The second case was one of cystitis following on measles, which passed into the chronic form; here also Salol did good service.

In writing on "The present position of the treatment of Cystitis" (*Therap. Monatsh.*, 1887, No. 2) Dr. Leopold Casper, Berlin, alludes at length to the effect of internal medication with antiseptics, and characterises Salol as one of the best. It was ordered in powder form with sugar 1½—2½ drms. *pro die*.

A decidedly favourable issue was attained by Dr. B. Arnold (*Ibid*, 1888, No. 7) in the case of an old man of 80 years suffering from paralysis of the expulsory muscles. The constant use of the catheter was followed by cystitis, the urine being alkaline, turbid and containing blood and fatty substances. These abnormalities of the urine persisted in spite of all measures, until finally 15 grns. of Salol was prescribed twice, and later—as the compound was well borne by the stomach—three times a day.

During the daily dosage of 30 grns. the urine gradually cleared up, and when the quantity was increased by another 15 grns. it exhibited at first a blackish green tinge, and then rapidly became clear; the sediment also steadily decreased in amount.

By continuing the use of the remedy, the diseased symptoms were kept in abeyance, but any suspension of its administration was followed by a return of the turbidity, etc.

The author observed that the small dose of 45, and then 30 grns. daily, had the desired effect of preventing the ammoniacal fermentation of the urine in the bladder, and so keeping it clear and acid. At the

same time the remedy was very well borne; the tongue, previously thickly covered, cleared perceptibly, and the appetite decidedly improved.

The fact (1) that Salol was split up in the organism into its constituents, and (2) that it was excreted as salicyluric and phenyl-sulphuric acids in the urine, led to its employment for attaining antisepsis of the urinary tract by a number of French physicians also, whose results corroborated those of the authors above mentioned.

Salol has also been used with excellent results in the treatment of inflammatory processes of the urethra, both acute and sub-acute in character, due to micro-organic activity.

Dr. Ch. Talamon, of the Paris Hospital, tried Salol in blennorrhagia. In two cases scalding had lasted a week, with abundant green pus and nocturnal erections. By the second day of the Salol treatment the excretion was thinner, and the scalding removed; on the fourth the discharge was milky, and by the seventh only a drop of serous liquid could be obtained at the meatus by pressure.

In two other cases the discharge assumed a milky character three days after the administration of Salol. In all these instances the cases were recent, and had not been aggravated by the injections which always tend to perpetuate the discharge.

Dr. Hirtz, of the same Institute, recorded similar results. In 20 cases the remedy checked the discharge at the end of a period varying from eight to twelve days. The analgesic action was manifested early in the history of the cases. By this author the combination of Salol and copaiba balsam or sandal-wood oil was largely prescribed (*v.* p. 91).

Dr. Dreyfous treated seven cases of gonorrhœa with Salol in doses of 1¼—2 drms. (*Brit. Med. Journal*, 1889, Dec. 7th). The discharge became less abundant, and in some cases a cure was effected in a few days. The remedy was sometimes given alone and sometimes combined with copaiba and cubebs in order to hasten the cure. Dr. Dreyfous recommends Salol to surgeons about to operate on the urinary organs; it rendered the urine aseptic and innocuous when it came in contact with wounded surfaces.

Mr. J. Ernest Lane, F.R.C.S., Out-Patient Surgeon of the London Lock Hospital, gave the results of the administration of Salol in fifty

cases of gonorrhœa (*Lancet*, 1890, March 22nd); six were cured, 24 showed considerable improvement, 15 showed no change either one way or the other, and in five the symptoms were aggravated. The doses used were from 5—30 grns. taken three times a day, and the beneficial effects manifested themselves in a very short time.

When improvement took place, the symptoms abated in from two to seven days; painful micturition was early alleviated, and, in cases of more chronic nature, the discharge was materially lessened.

At first the author used injections at the same time as the Salol was given in five-grn. doses, but, subsequently, he raised the dosage to 10, 20, and in a few cases, 30 grns., and relied upon it exclusively. Out of 40 cases so treated, improvement was noticed in 20 within a week, while, as already stated, six were completely cured. The author believed that, in chronic cases, the cure would be materially hastened by an astringent injection, and that more favourable results would have been obtained had larger doses been used from the beginning.

Dr. William White described before the American Syphilographical Society his experience with Salol in over 50 cases of inflammation of the urethra. In 35 of these the discharge was completely arrested at the end of a week.

Interesting cases, which may be classed under this heading, were described by Dr. Vernon Jones in the *British Medical Journal*, 1892, Feb. 13th. In the first, the patient, who had suffered from gonorrhœa for some time, strained his knee slightly, in consequence of which there was great pain and effusion into the joint; the limb was put on a splint, and all the usual remedies tried, without avail. The urethral discharge continued, and the other knee also became involved. He was then put on 15 grns. of Salol three times a day, and from that time improvement set in; the discharge diminished, pain ceased, and eventually, by the aid of local measures, the effusion also subsided.

The second case was less instructive, as the author did not rely upon Salol alone, but changed about with other agents. The case recovered in the end. In the third instance recorded by Dr. Jones, the patient was a woman, and, as might be expected on theoretical grounds (from the shortness of the urethra), the action was very much less marked in the female sex.

3. In Diseases of the Intestinal Tract.

In the account of the employment of Salol given by Dr. Georgi in the *Berl. klin. Wochenschr.*, 1887, Nos. 9-11, already referred to, there is a section devoted to the consideration of the value of the remedy in diseases where intestinal antisepsis is indicated. He found that beneficial results were produced.

Dr. E. L. Vansant, Demonstrator of Pathological Histology, and Chief of the Medical Clinic, Philadelphia, gave an account (*Medical Times*, 1888, Oct. 15) of some dozen cases of diarrhœa and dysentery treated by him with Salol, sometimes alone and sometimes with bismuth subnitrate. The patients were of very varied ages, from 10 months up to 57 years, but in every case the remedy was well borne and successful in bringing about the desired results. It was found that much better results were obtained by prescribing the Salol every three hours than by restricting it to three times a day.

Dr. R. B. McCall (*St. Louis Medical Brief*, 1888, Nov.) detailed a case of dysentery in a delicate boy of five years. At first the fluid extract of ergot did good, but delirium ensued, and so it was substituted by subnitrate of bismuth combined with paregoric. This seemed to be having a good effect for a day or two, when the disease suddenly resumed its first serious character. Then small doses of calomel (¼ grn.) with 1 grn. of Dover's powder every five or six hours, was prescribed, but obliged to be given up because of the nausea produced. Under routine methods it was plain the boy could not be saved, and Dr. McCall resolved to essay Salol. He ordered it in 2-grn. powders every three hours, and by the end of the first day there was evident improvement in the character of the evacuations, diminution in their number, fall of temperature, and slowing of the pulse; at the same time restlessness and fretfulness vanished as if by magic. After the second day the dose was increased and improvement continued, fever entirely disappearing, the tongue cleaning and appetite returning.

In about 10 days nearly 200 grns. of Salol were taken by this child without the least sign of oppression, disturbance of any kind, of

stomach, heart, kidneys or brain. The author expressed the conviction that Salol was perfectly safe in suitable doses at any age.

Theoretical considerations induced Dr. A. H. Goelet, New York (*Medical Journal*, 1887, Aug. 6th) to prescribe Salol in a bad case of diarrhœa where bismuth, extract pancreatis and sodii bicarbonas, with a milk diet, had proved ineffectual. Ten grns. of the remedy were ordered to be taken every two hours. By the next morning the patient reported himself all right. The motions ceased after the second dose, as well as the pains and colic. A dose an hour before each meal for two days was ordered with a practically unrestricted diet. The motions continued natural in character and number, thus proving that the remedy had no constipating effect.

In a second case a fifteen months' child suffering from diarrhœa and vomiting, one grn. was ordered every two hours dry on the tongue with a teaspoonful of water after it. The vomiting ceased immediately, and in six hours the diarrhœa had ceased as well; on the next day the stools were natural, and the Salol was discontinued.

The author expressed the opinion that Salol was the only purely satisfactory remedy he had ever used in such cases. In typhoid fever, every three hours, there was nothing better, while he could not say that it shortened the attack, it annulled the excessively disagreeable odour of the fæces, and relieved the tenesmus and flatulence due to accumulated gases in the colon. He did not know of anything which so satisfactorily relieved flatulence of any origin.

Other cases in which Dr. Goelet successfully prescribed Salol were summer diarrhœa and dysentery of children; under such treatment, if seen early, and properly dieted, there was no need for apprehension.

Corroborative evidence was furnished by Dr. O. T. Osborne, New Haven (*New York Medical Journal*, 1888, April 7th). As indications for Salol in bowel troubles, he cited vomiting, purging, cramps, and all the symptoms of the so-called "summer diarrhœa" of children. He used it in twenty-two cases of all kinds, including one of acute dysentery, without a single failure. The dysenteric patient had as many as sixty bloody and mucous stools daily. The treatment was four grains of Salol internally every two hours with morphine, whiskey

and ice-water injections into the rectum. These latter failed, however, to relieve the tenesmus or sanguinolent nature of the stools, and were therefore substituted by a four per cent. solution of Salol in alcohol, two teaspoonsful in water being injected as soon as the tenesmus was felt to be coming on. Immediate relief followed the first injection, and the next day no blood was passed, but fæcal matter appeared in the stools.

Except in a single case where an eruption occurred after the use of Salol—which could not be certainly traced to the remedy—there were no unpleasant symptoms due to its use. All the patients, save the dysenteric, were cured without opium, and indeed without any other medications at all, except the Salol. Although it is insoluble in the gastric juice, the compound allayed vomiting; this effect, conjectured Dr. Osborne, might be due to an antiseptic action of Salol *per se*.

Dr. Kimura, whose paper on the use of Salol has been already referred to, used the remedy against dysentery with good effect. About five grns. were emulsified with water and injected into the rectum; the most satisfactory results followed when the injection was preceded with two or three quantities of lukewarm water.

Dr. Hirtz prescribed Salol in combination with salicylate of bismuth in 35 cases of typhoid fever with great benefit. Combined with bicarbonate of soda, it arrested eructations, pyrosis, flatulence and diarrhœa, so often witnessed in dyspepsia, due to dilation of the stomach. The remedy was always well borne and had the advantage in typhoid of effecting antisepsis simultaneously of the intestinal and urinary tract. Similar results were obtained by Hesselmann.

In a lengthy treatise on "Intestinal Antisepsis" (*Therap. Gazette*, 1891, Aug.) Prof. Dujardin-Beaumetz recommended Salol particularly as the best of intestinal antiseptics. He prescribed it for rectal cancer with bismuth salicylate and sodium bicarbonate in five-grn. doses before breakfast and dinner. He added, however, that the dose of Salol might be increased to a drachm daily.

Dr. M. H. Fussell devoted an entire paper to the recording of his experience with Salol in diarrhœa (*Therap. Gaz.*, 1892, p. 508) and

generalised his results as follows:—

1. Diarrhœa due to dietetic error, and that which is common in adults and infants in summer, is well controlled by the administration of Salol and bismuth or chalk.
2. Opium is rarely necessary where Salol is used.
3. Salol controls the abdominal pains equally as well as opium.
4. It is perfectly safe, having no bad after-effects.
5. It is especially useful in the diarrhœa of children.
6. It constantly corrects the fœtor of the stools.

Dr. Mensi also adds his testimony to the value of Salol in the diarrhœa of children (*Therapist*, 1892, Oct. 13th). Complete recovery was obtained, with a single exception, by the use of Salol in 27 children suffering from the chronic form of the affection. The daily dose to young children was 4—8 grns; to elder children, 16—30 grns.

4. Salol in Cholera.

It was shown by Dr. W. Löwenthal (*Le Progrès Méd.*, 1889, No. 2) (1) that the comma bacillus formed toxic ptomaines with the pancreatic juice, and (2) that the process of their formation could be prevented by addition of a small quantity of Salol. Since this latter was harmless to man, the author recommended it for the treatment of cholera, and the suggestion was followed by Dr. Ferd. Hueppe, who prescribed it in combination with bismuth salicylate, and reported encouraging results from India.

Dr. James Couldrey (*Brit. Med. Journ.*, 1892, Aug. 6th) also recommended Salol against cholera, suggesting its prescription with tincture of chloroform and morphine internally, with hypodermic injections of ether in the relapse stage.

Dr. Salvator, of Zambeles, Phillipine Islands, sent Prof. Löwenthal the record of 53 cases of cholera treated with Salol. Only three—received in very advanced stages of the disease—terminated fatally. Doses of 30 grns. were first given, followed by further doses of 8—15 grns. every hour or half-hour.

5. In Yellow Fever.

During an epidemic of yellow fever in Rio de Janeiro, Dr. Ferreira tried Salol, being led to do so by the theoretical considerations based on the symptoms of the disease, and on post-mortem revelations. He reached the conclusion that the fever was intestinal in origin, and his experience with Salol appeared to confirm the theory in the most positive manner. He prescribed it in doses of five grns. every two hours in water, and regarded its value as beyond doubt, though the number of cases in which it was tried was not large. Further trials with Salol in this disease could not fail to be interesting, though it seems that it must be given in considerable doses if success is to be attained.

6. In Leprosy.

In the Biennial Report of the Board of Health to the Hawaiian Government, Dr. Lutz, of Honolulu, stated that he had obtained a very favourable impression as to the value of Salol in leprosy. In half a dozen cases the leprous fever was almost immediately interrupted by the daily use of 1½—2 drms. divided into three or four equal doses. In some cases the acute eruptions immediately and quickly disappeared under the use of Salol, leaving the patient in complete health during the next six months' observation. In another case a few tubercles appeared, and even persisted during the use of the remedy, but the author believed these would probably have been prevented by the use of larger doses.

7. For Diagnostic Purposes.

Salol has done good service in the diagnosis of morbid conditions of the upper digestive tract. This employment of the compound depends upon the fact that it passes unchanged through the stomach, and is resolved into its constituents and absorbed only in and from the intestines. Drs. Sievers and Ewald established that in healthy individuals an hour is the extreme limit between the taking of the dose

and the appearance of salicylic acid in the urine. Variations from this standard would be due to pathological causes. On this basis the diagnosis of changes in the motor efficiency of the stomach could be readily and reliably made with the help of Salol.

Thus occlusion of the pyloris was successfully diagnosed in a case where, after administration of Salol, no salicylic acid appeared in the urine (*Brit. Med. Journ.*, 1890, June 14th), and Drs. Sievers and Ewald were able, in a number of instances, to diagnose in this way dilatation and functional disorder of the stomach.

EXTERNALLY.

1. In Surgery and Skin Affections.

It will be unnecessary to reproduce extracts from all the literature which has appeared upon the external application of Salol. As a substitute for iodoform, the chief advantages which it has manifested are—

1. Freedom from odour.
2. Almost absolute non-toxicity.
3. Valuable drying properties.

Dr. Eugen Grätzer, Menchi (*Therap. Monatsh.*, 1884, No. 9), Corner (*Journ. Amer. Med. Assoc.*, 1889, June 8th), Saalfeld, etc., observed that when applied to raw or excoriated surfaces, it exerted a powerful antiseptic and anodyne action. It was used in surgery in the form of powder, either alone or mixed with starch or French chalk, as liniment. Professor Demme obtained very good results in burns; Dr. Grätzer and others in abscesses of the leg and sycosis parasitaria; Saalfeld in impetigo, eczema; and Professor Barduzzi in various skin affections, especially those of syphilitic origin.

Very careful researches into the action of Salol externally as an antiseptic were carried out by Dr. M. G. Patein (*Surgical Review*, 1887, p. 519), who recorded its successful use in localised tuberculosis, in the treatment of variolous pustules of the face (20 per cent. solution in ether), and other diseases of a similar nature. In cases of epithelioma of the nose, fistula of the breast, mammary and maxillary

abscess, removal of diseased growths, caries of the sternum and rectal abscess, the results were superior to those obtained with iodoform. In an operation for a laryngeal cyst, requiring tracheotomy, the action of Salol was remarkable.

Dr. M. Perrier observed very good results in local tuberculosis; where the bones were the seat of disease, this surgeon discarded iodoform and used Salol alone. In several cases he filled the cavities with gauze sachets containing varying amounts of Salol powder without producing any symptoms of poisoning, while all septic action was arrested.

2. In Rhino-larynology.

The successful treatment of 22 cases of inflammation of the soft palate, of tonsillitis and pharyngitis by Salol was reported by Dr. Gougenheim. Dr. Caport (Brussels) first called attention to the remarkable value of Salol in the treatment of suppurative tonsillitis, and the publication of his results led Dr. Gougenheim to test its value in various forms of angina. On account of its insolubility, the remedy was conveniently dispensed in mucilage 15—20 grns. three times a day, and the diet almost exclusively restricted to milk. In all the author's cases the dysphagia was cured with the most remarkable rapidity, no matter what its cause.

Dr. Otto Seifert (*Centralbl. f. klin. Med.*, 1887, No. 14) tried Salol in the local treatment of diseases of the mouth, nose, and larynx. He praised it highly as a mouth wash and gargle—one teaspoonful of a six per cent. alcoholic solution in a glass of warm water—in stomatitis, ulceration of the mouth and pharynx, angina; in chronic diphtheria the remedy did better service than potassium chlorate and salicylic acid.

Dr. Thorner, Cincinnati (*Lancet Clinic*, 1887, Dec. 10th), characterised Salol as far superior to sodium salicylate, not only in certainty and rapidity of effect, but also as regarded the relative smallness of the dose. In those exceedingly painful cases of acute catarrhal pharyngitis, involving the entire muscular system of the neck, the pains rapidly disappeared under the use of 9—12 grns. of Salol three

times a day. The effects were nearly equal in phlegmonous and follicular angina, pain disappeared after a few doses, the restless patients fell into a refreshing sleep and were enabled to swallow almost without pain.

Good results followed the internal use of Salol in nervous otalgia, as well as in one case of otitis med. chronica purulenta.

In ozæna, Cozzolina recommends insufflation of a Salol powder (30 per cent.) in combination with boric acid (15 per cent.), salicylic acid (3 per cent.) and French chalk, with a minute quantity of thymol.

In the treatment of diseased condition of the mouth with fœtor, Georgi recommended a mouth wash made by mixing 2—2¼ drms. of a four to five per cent. alcoholic solution with six ounces of water.

FORMULÆ AND METHODS OF USE.

When prescribed as powders the slight taste of Salol may be masked by oil of peppermint. As already repeatedly stated above, it has also been given in wafers and emulsion.

When given in diseases of the genital tract the solubility of Salol in essential oils and oleo-resins enables it to be readily combined with sandal-wood oil or balsam of copaiba. The employment and efficiency of these combinations has been already described.

Externally in ulcers, skin affections, etc., the oleaginous solution is effective, or an ointment (1—10 per cent. with lanolin). When employed as a dusting powder it is best mixed with starch or French chalk.

As a topical application against rheumatism it has been recommended to dissolve four parts of Salol in an equal weight of ether and add 30 parts of collodion. Painted on the affected areas this application is a useful adjunct to the internal treatment.

SALICYLIC ACID AND ITS SALTS.

The value of Salicylic acid in the various forms of the rheumatic diathesis needs no emphasis; it has obtained a well-recognised position as possessed of what may be termed specific virtues in the treatment of the class of affections above-named.

The reputation of the substance and its preparations was largely built up upon results obtained with the product derived from the vegetable kingdom, and especially from the oil of wintergreen, and when Kolbe's method of synthesising Salicylic acid was first used for the preparation of a medicinal article, doubts were entertained as to its exact correspondence with the natural product.

Chemical investigation did show, as a matter of fact, that commercial Salicylic acid contained foreign acids, and physiological work carried out by Prof. M. Charteris and Dr. W. Maclennan indicated that a dangerous and even fatal action on animals was produced by these foreign constituents of the synthetical acid. Professor Charteris extracted a substance from the acid which in doses of one grn. proved fatal to a rabbit of 2 lbs. weight. At the same time it was proved that it was possible to purify the acid, and the physiological action of the substance, thus freed from impurities, was not characterised by any of the symptoms of paralysis or even of depression observed to follow the administration of the impure article.

In consequence of this work Messrs. Schering turned their attention to the subject, and adopted additional means of purification. Some of the product of the modified process of manufacture was placed in the hands of Prof. Charteris, who examined it physiologically, and stated that he satisfied himself it was precisely similar to the acid obtained from natural salicylates, and therefore of such purity as to be equally eligible for medical use.

Subsequent researches, chemical and physiological, proved beyond doubt that the Salicylic acid and salicylate of sodium, prepared by the improved process referred to above were absolutely free from foreign acids or other impurities, and consequently that they were indistinguishable in their action upon the animal organism, whether in health or disease, from the compounds obtained from natural sources.

Since the salicylates provided by nature are far from abundant and difficultly isolated, so that high prices follow as a matter of course, the importance of a means of artificially preparing them which is comparatively simple and unlimited in productive capacity is self-evident. But also it is essential that the synthetical body should be absolutely pure, not only to chemical but to physiological tests as well. The researches of Professor Charteris and the other workers have had a very practical and valuable outcome in leading to the manufacture of a Salicylic acid and compounds which can be used in every way as freely and harmlessly as the preparations obtained from the vegetable kingdom.

BISMUTH SALICYLATE.

Basic salicylate of bismuth is a definite compound with the formula $Bi(C_7H_5O_3)_3\,Bi_2O_3$ containing 76 per cent. of bismuth oxide and 23 per cent. of Salicylic acid. It occurs as an amorphous yellowish white powder, entirely insoluble in water.

Under the name salicylate of bismuth, however, preparations have been introduced into medicine which were little else than mixtures of Salicylic acid and oxide of bismuth; as the free acid has a well-marked irritant action when externally employed, it is necessary to avoid the use of these articles.

It should be noted that neither water, alcohol, ether, nor chloroform, should extract anything from the true salicylate of bismuth. Preparations which contain free Salicylic acid yield it to these solvents and are thus detected.

The compound has been employed in medicine as a substitute for iodoform in the treatment of wounds, ulcers, etc. Its value in these

cases depends upon the following properties:—

1. It is antiseptic, rapidly removing fœtor and arresting morbid process due to micro-organic activity.
2. It is drying, diminishing secretion, and thus indirectly checking bacterial development.
3. It is soothing and healing, healthy granulations quickly forming during its use.

In internal antisepsis salicylate of bismuth has also played an important part, both alone and in combination with other remedies of the same class. Vulpian recommended it highly in morbid conditions of the intestinal tract, especially of the rectum, and Dr. Solger used it in affections of this kind with great success.

The best results were obtained in irritated and sub-inflammatory conditions of the intestines, in which its mild antiseptic action gave it great advantages over the nitrate of bismuth previously employed.

The pure bismuth salicylate, free from uncombined acid, is well borne by the stomach, and can be continuously given for months without ill-effect. It is, therefore, specially suitable in chronic diarrhœas, even when of most obstinate nature. Surgeons have also found it useful to prescribe after operations upon the intestines, in order to prevent fæcal accumulation and development of gases which endanger the results of the operations.

Dr. Dujardin-Beaumetz recommended bismuth salicylate (*Therap. Gazette*, 1891, Aug.) combined with equal doses of Salol in the treatment of rectal cancer. He prescribed five-grn. doses of each of the remedies to be taken before breakfast and dinner; the adjuncts to this treatment were antiseptic rectal irrigations and a vegetarian diet. Where the disease did not cause much local constriction he believed quite satisfactory results could be obtained from the means indicated.

LITHIUM SALICYLATE.

This compound is a white crystalline powder, soluble in little more than its own weight of water; it is also abundantly taken up by alcohol.

The lithium salts have, as known, been used for years in the treatment of gout and of diseases of the urinary tract. Salicylic acid also won a high reputation in the treatment of many similar affections, and, therefore, its combination with lithium promised to display therapeutical properties most valuable against the uric acid diathesis.

Clinical trials with lithium salicylate showed that the expectations formed as to its value were well founded. It manifested very valuable properties in the treatment of acute rheumatism and the various affections due to, or associated with, an excess of uric acid in the blood.

Unlike the salicylates of the commoner alkali metals, lithium salicylate does not produce any disagreeable effects upon the digestive organs. The tendency of the ordinary salicylates to do this is a contra-indication to their use in some cases, and in these especially lithium salicylate appears to be very suitable. Over the carbonate of lithium the newer salt has the advantage of being readily soluble, and, therefore, its absorption and therapeutical effect are the more reliable and prompt. The property of dissolving readily and entirely in water is characteristic of the pure salt, and will serve as a rough test.

Dr. Vulpian found lithium salicylate equal in every case to salicylate of sodium as regarded therapeutical effect, while, in some instances, it was distinctly more efficient. This was especially noticeable in some cases of acute rheumatism of the joints; occasionally, in this affection, the fever, though at a very low level, is difficult to entirely remove, and sodium salicylate is by no means always successful, even when its administration is long continued, in bringing about complete apyrexia. In these cases the lithium salt proved especially valuable.

In the chronic form of rheumatism, and particularly in rheumatic affections of the tendons, lithium salicylate proved superior to the sodium salt.

The medium daily dose for adults is one drm., though it may be increased to about 1½ drms. *pro die* without any disagreeable results. The compound appears to be worthy of more extended trial than it has hitherto received, as it possesses a valuable combination of therapeutical virtues with a noteworthy absence of drawbacks.

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STRONTIUM SALTS.

Hitherto the so-called alkali earth metals have not yielded salts of very marked therapeutical value, or, at any rate, where such have been prepared and employed in medicine, their usefulness has depended more upon the acidulous group in the salt than upon the metal itself. This is easily verified in the case of such compounds as calcium iodide, hypophosphite, etc. The barium compounds are well-known to be characterised by a powerful poisonous effect, specially manifested upon the circulatory system, and therefore they have been little or not at all used.

The close chemical relationship existing between Strontium salts and those of barium, as well as the difficulty of obtaining the former perfectly free from traces of the poisonous barium compounds, led to the impression that the Strontium salts were possessed of similar dangerous properties.

Original investigations recently carried out in the hospitals of Paris, and communicated to the French Academy of Medicine and to other learned Societies, have conclusively proved that the

Strontium Salts are innocuous,

and not only so, but that they have a beneficial influence upon the nutritive processes.

The first evidence of this kind was contained in a treatise by Ismael Nassan, the effect of which was to lead to the preparation of absolutely pure salts for use in medicine. These were employed therapeutically by a number of experimenters, and with so much success as to be considered worthy of special notice and emphasis.

THERAPEUTICAL USES.

Bromide of Strontium.—This compound was found to have all the useful properties of the alkaline bromides without their tendency to produce digestive and nutritive disturbances. Dr. Constantine Paul prescribed it in daily doses of 1½ drms. to a young girl suffering from hystero-epilepsy. Although the attacks had resisted potassium bromide given perseveringly in drachm doses, they were entirely arrested by the Strontium salt and did not recur.

Bromide of Strontium was prescribed by Deny for seven epileptics, and under this treatment the patients had among them 246 attacks in seven months. During the corresponding period of the preceding year bromide of potassium had been administered, and the number of attacks was 331, consequently the Strontium salt reduced the fits by more than a quarter. Both compounds were given in exactly the same doses. One of the patients who was most benefited by the Strontium treatment, ceased to suffer from the maniacal excitement after each epileptic seizure to which he had previously been subject.

From the experience of Féré and Prof. Germain Sée, it appears that pure Strontium bromide has no disastrous effect upon the stomach, even when given in large doses. The latter authority employed the salt with success in various gastric affections, and it also proved useful in diabetes, causing a diminution in the amount of sugar excreted.

Lactate of Strontium.—Dr. Laborde first recorded the beneficial action of this salt in obstinate painful dyspepsia, and his observations were subsequently confirmed by other experimenters. Dr. C. Paul found that it was well borne in daily doses of 2—3 drms., and employed it with advantage in visceral congestion, and in Bright's disease; better results were obtained than with lithia. Though not a diuretic, Strontium lactate brings about at once a diminution in the amount of albumen excreted, and correspondently improves the collateral symptoms. When the administration of the remedy was suspended, the albumen reappeared in the urine, to again fall to zero when the treatment was resumed.

Other affections of the urinary system associated with excretion of albumen were similarly benefited. Dr. Dujardin-Beaumetz reduced the proportion 50 per cent. within one to four days. He characterised the salt as a valuable agent, both reliable and harmless. Laborde prescribed the lactate as a tænifuge with success in drachm doses repeated daily for about a week.

Other Strontium Salts which have been successfully used therapeutically are the iodide, a one or two per cent. solution being employed in scrofulous diseases; the nitrate, given in doses of ½—4 drms. in articular rheumatism; the phosphate, regarded by Laborde as one of the most valuable nutritive and tonic medicaments known; and the acetate, which has also a reputation as an active tænifuge. Altogether there is sufficient evidence that, if perfectly pure Strontium salts are employed, they will prove a valuable enrichment of materia medica, and increase the power of the physician to control certain obstinate and obscure diseases.

POTASSIUM BROMIDE.

Although of late years materia medica has been enriched by a considerable number of synthetical hypnotics and sedatives, which may be described as products of organic chemistry, yet Bromide of Potassium maintains its position as a most valuable remedy in nervous diseases, whether due to abnormalities of the nerve centres themselves, or to excessive reflex sensibility.

It is necessary, however, to call attention to the desirability of care in the selection of Potassium Bromide for use in medicine. The standard to be aimed at is, of course, absolute purity, not only on economic grounds, but because scientific medicine can only be based upon the presumption that the substances administered or applied are of definite composition and perfect purity.

Chemical analysis has shown, however, that there are brands of Bromide of Potassium which are far from satisfying the requirements of the high standard alluded to. The examination of commercial specimens of the salt, carried out by Messrs. Helbing & Passmore, showed that there are American brands which contain notable amounts of impurities in the form of combined chlorine.

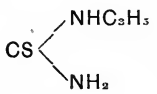
It is therefore necessary for prescribers and dispensers to exercise care in the selection of Potassium Bromide for therapeutical use, in order that the physician may be able to rely upon the constancy of effect of the remedy he prescribes. Physiological research has shown that apparently quite insignificant doses of compounds may have an appreciable effect upon the organism, and there is sufficient difference between the action of chlorides or bromates (another possible contamination of commercial bromide) and bromides to render it undesirable to administer a preparation which contains a relatively large proportion of these compounds as impurities.

THIOSINAMINE.

This substance is one of a group of bodies which may be regarded as derivatives of urea. Systematically it is termed allylthiocarbamide—a name which indicates that in the urea nucleus the oxygen atom is replaced by sulphur. The place of the allyl group in the body might be occupied by almost any compound radical such as phenyl, ethyl, etc., and most of the possible combinations thus brought about have been experimentally examined physiologically and bacteriologically.

On the whole, Thiosinamine proved the most valuable member of the group.

A lengthy treatise on the employment and action of the compound has been written by Dr. H. v. Hebra. In this paper the formula of Thiosinamine appears as—



and it is described as prepared by acting on volatile oil of mustard with ammonia in the presence of alcohol. As in the case of most derivatives of mustard oil, water decomposes the compound, and consequently alcohol or ether must be resorted to for the purpose of preparing solutions of Thiosinamine. Such solutions administered subcutaneously produce a smarting sensation, but this appears to be of very short duration, and not sufficiently unpleasant to make patients unwilling to persevere with their use.

THERAPEUTICAL USE.

Some three years ago Dr. v. Froschauer stated that animals could be rendered immune to bacillary infection by subcutaneous injection

of allylsulphocarbamide. Careful repetition of the experiments showed that this was not well-founded, but at the same time led to the employment of the compound in some chronic cutaneous diseases.

The medicinal value of Thiosinamine was made the subject of careful study by Dr. Hebra. He found that a prominent feature of its action was a well-marked local reaction, not accompanied by any general constitutional disturbances.

About two hours after the injection the affected site reddened and began to swell, the intensity of these symptoms depending upon the extent of the disease and the dose injected. After some four or six hours these phenomena subsided, and the normal colour was regained about 18 to 20 hours later. No vesicles or serous exudation was ever observed.

The majority of cases treated were lupus of various severity and site. On the day following the reaction considerable desquamation occurred, and all the diseased patches were covered with scales; the adjacent healthy skin remained smooth and unaltered.

As regarded the beneficial effects of the treatment a few injections were sufficient to render this unmistakable. Lupus tumidus became much less prominent, the whole area sinking considerably, while in the ulcerated form the thickened margins decreased, and in a few weeks' time the healing process was established, after vain endeavours to effect it by external remedies.

The lupoid nodules offered the greatest resistance, owing, doubtless, to the paucity of the blood supply.

The results, as regarded the cicatricial tissue following the spontaneous ulceration of lupus, or the application of caustics, were much more striking. Whenever such tissue disturbed nutrition or impeded movement, a complete softening and loosening was brought about by the medication. Very striking cases, illustrative of this fact, are described by the author.

Other cases in which favourable results were attained by the use of Thiosinamine were those of chronic glandular swellings. Syphilitic affections of the glands were not affected, and it was suggested that this fact might be made use of for diagnostic purposes.

On the day of injection an excess of 7½—18 ounces of urine was passed, but no untoward effect upon the kidneys was ever observed; neither albuminaria nor any other morbid changes were detected, though carefully watched for. The process of absorption generally was promoted.

All the patients felt well during the treatment. Appetite increased remarkably in every case, and coincidently with the administration of the remedy; as a natural consequence, nutrition and general body-weight also improved. Experiments made on animals showed that doses ten to twenty times as large proportionately as those given to the human subject, caused only a slight lowering of the blood-pressure, which was probably due to the solvent.

Dr. Hebra recommended that only old processes should be treated with Thiosinamine, save in lupus and allied conditions. Carefully employed, it seems to have a valuable action in clearing nebulæ of the cornea.

DOSAGE.

A 15 per cent. alcoholic solution was employed, two or three divisions of a Pravaz syringe being injected twice weekly, so that 5—7 grns. of Thiosinamine were administered at each injection. In cases of lupus the dose was increased in the third week to half a syringeful, and in the fourth or fifth week to a whole syringeful of 15 per cent. solution. In a few cases even more was given without bad effect.

DIABETIN.

The fact that the sugar excreted by diabetics is identical with ordinary dextrose or grape sugar has always been held a sufficient reason for cutting off from the dietary of such patients not only all preparations containing dextrose, but also all farinaceous or starchy foods which are known to be converted into that sugar by the action of the digestive ferments.

To a large proportion of diabetics this restriction is a considerable hardship, and numerous attempts have been made to substitute ordinary sugar by some preparation which, while satisfying the craving of the patients for sweetness, should at the same time be free from any tendency to aggravate the disease.

The most successful of these substitutes, the benzene derivative termed "saccharin," though meeting the latter requirement, since it passes through the system unchanged, does not satisfy the craving for the natural saccharine substance, sugar, because its taste is altogether different to this. The sweetness of "saccharin" has a cloying, nauseating character, that generally leads to its speedy abandonment.

Although the chemical laboratory has failed then to satisfactorily solve the difficulty alluded to, yet such an enormous variety of sweet compounds is elaborated by Nature that it was recognised as extremely probable that some of them would be suitable for the purpose in view.

The true sugars have, as known, a very close relation to one another in chemical composition, but the progress of the study of the alliance of chemical structure and physiological action has revealed the fact that apparently insignificant constitutional differences are accompanied by the widest variations of medicinal action.

Now dextrose, the sugar which appears in the urine of diabetic patients, is one member of a group of compounds very closely allied

among themselves, but also exhibiting certain important differences. Lævulose is another member of the same class which, in constitution and general reactions, is very similar to dextrose. Yet experiment has shown that, as regards physiological destiny, when introduced into the animal organism, the similarity does not hold, and for this reason it is probable that lævulose will be available for use by diabetic patients without aggravating the disease from which they suffer.

But although lævulose or "fruit sugar" is moderately abundant in the vegetable kingdom, either free or combined, yet its preparation in the pure state has presented very great difficulties. The only form in which it was known, even to the chemist, was that of a sticky syrup that could not be induced to crystallise, and was rarely colourless.

It may therefore be regarded as a triumph of technology, that a method has now been elaborated, by which this sugar is obtained as a pure white crystalline powder, as convenient for general use, as a food-stuff, as any other of the sugars. This pure substance is distinguished from the older product known as lævulose, by the name Diabetin.

The exact value of Diabetin, as a sweet food for diabetics, can of course only be arrived at by an examination of its effects in a considerable number of cases under experienced guidance. For this purpose the attention of physicians is called to the preparation, so that trials with it may be at once instituted, and the results recorded in medical literature.

At present, as a matter of course, Diabetin cannot be produced at anything approximating to the price of ordinary cane sugar; but, nevertheless, it can be produced at a figure which places it within the reach of the majority of patients.

IODOFORM.

It is well known that Iodoform, as ordinarily prepared, is obtained from raw materials which inevitably vary in quality, and by the assistance of different solvents for the purpose of recrystallisation.

The effect of these varying factors upon the appearance and even quality of the product scarcely needs pointing out. That differences in the purity of the materials from which a substance is prepared, result in corresponding variations in the purity of the product, is generally self-evident, and a very little consideration shows that where processes are not precisely similar, exact resemblance is not to be expected in the compound produced.

Thus, in the case of Iodoform, the size, manner of aggregation, or even form of the crystals, may depend upon the solvent employed, while further, this factor has often an appreciable effect in modifying the odour of the product, owing to the difficulty of removing the last traces of the mother liquor.

Modern progress in technical chemistry has been largely along the lines of increasing the purity of the compounds manufactured, by means of more refined methods of preparation or of purification, or both. At the same time the practical applications of the various forms of electricity have enormously increased, and it has been found possible, by means of this force, to achieve results in numerous fields which previously were unattainable.

The dynamo-electric current was pressed into the service of the chemical manufacturer some time ago, experiments being made to ascertain the practicability of its employment for the preparation of fine chemicals, and to compare the quality and appearance of the products with those of the ordinary chemical processes.

Among the compounds experimentally manufactured in this way was Iodoform, and the results in this case were regarded as being of

special interest, owing to the peculiar nature and importance of the substance.

The new process started with absolutely pure materials instead of the ordinary crude substances. Perfectly pure iodide of potassium was the one reagent and the purest absolute alcohol (unmethylated, of course,) the other. The interaction of these compounds, which, as known, have not, under normal conditions, any noteworthy tendency to react, was brought about by the dynamo-electric current.

In this way Iodoform separated immediately in a state of absolute purity, and so perfect in every respect that recrystallisation proved unnecessary. Further, the product was found to be always absolutely uniform in character, as indeed was to be *a priori* anticipated from the premises that it constantly separated under precisely similar conditions.

"Electrolytic Iodoform," as it may be termed, has the form of lemon yellow, soft and delicate scales, characterised by the absence of sharp or hard edges. The odour is absolutely free from all pungency, and can be described as mild compared with that of ordinary commercial iodoform.

As regards its chemical nature, the product corresponds to a body represented exactly by the formula CHI_3. It stands the most searching tests of those Pharmacopœias which demand the highest standard of purity. In its original form it can be applied in medicine and surgery without producing the irritant effects of the ordinary product (owing to its softness and delicacy), and if desired in a powdered form can be readily reduced to an impalpable condition of fineness.

CRESIN.

In the course of the exhaustive bacteriological researches which have been made upon the compounds of the aromatic series of hydrocarbons, it was found that the higher homologues of phenol, termed "cresols," were more powerful disinfectants and antiseptics than phenol itself. At the same time the noteworthy observation was made that these compounds were free from the pronounced poisonous properties of carbolic acid.

The natural conclusion was, therefore, that the cresols were much more suitable for use as disinfectants than phenol and its derivatives. But though this was undoubtedly the case, a serious practical hindrance to their employment was found in the fact that they were very slightly taken up by water.

This difficulty did not seem at first likely to be easily overcome, and consequently, for some time after the powerful antiseptic virtues of the cresols were discovered, the substances were not actually made use of in therapy.

Accepting as almost insuperable the difficulty of getting the cresols into solution in a form suitable for medicinal application, efforts were made to render them available for use by emulsification. The products thus obtained were, however, not free from objections, apart from the fact that they did not really solve the problem of rendering the cresols capable of employment in *solution*—the only form in which their pronounced germicidal properties could be taken advantage of by the physician in their peculiar and unabated energy.

Subsequently attention was again directed to the desirability of getting the cresols into true solution, and by following the principle that the phenomenon of solution has often a close relationship with similarity of chemical nature, the problem was at length satisfactorily solved.

It was found on experiment that the cresols, so insoluble in water, were taken up by solutions of salicylates, of salts of oxybenzenecarboxylic acids generally, of oxybenzenesulphonic acids and other allied compounds.

These solutions had the great advantage of being neutral, and therefore specially suitable for use in surgery, etc., where of course liquids varying in any marked degree from neutrality are very objectionable.

Cresin is a solution of cresol in an aqueous solution of cresoxylacetate of sodium; it forms a clear brown liquid which contains 25 per cent. of the active ingredient. The cresol dissolved in this preparation is, as already stated, markedly less poisonous than carbolic acid, and yet at the same time its antiseptic power is four times as great as that of phenol.

On these grounds Cresin is an excellent disinfectant and antiseptic, which even in highly dilute solutions has a powerful deodorant action. In one per cent. solutions it has done good service for the disinfection of surgical instruments, of night-commodes, etc.

In the treatment of wounds and surgery generally, ½—1 per cent. solutions further healthy granulation, and promote healing by first intention without suppuration. Equally good results are obtained in the treatment of torpid ulcers of the feet of long standing. In these cases also ½—1 per cent. solutions may be advantageously used.

The preparation is also suitable for use in the local treatment of affections of the mucous membrane of the upper part of the respiratory tract. For such purposes its freedom from irritating and poisonous properties render Cresin especially useful. Solutions in water of the strength of ¼-½ per cent. form gargles which are efficient without being too unpleasant; the same liquids may also be employed as sprays or for inhalation with advantage.

Although the liquid is not recommended for internal use at present, it seems possible that it might be found suitable for employment in this way in certain cases. Apart from the general fact that the cresols are free from marked poisonousness, actual experiment has shown that half a drachm given to a rabbit did not produce any functional disturbances whatever.

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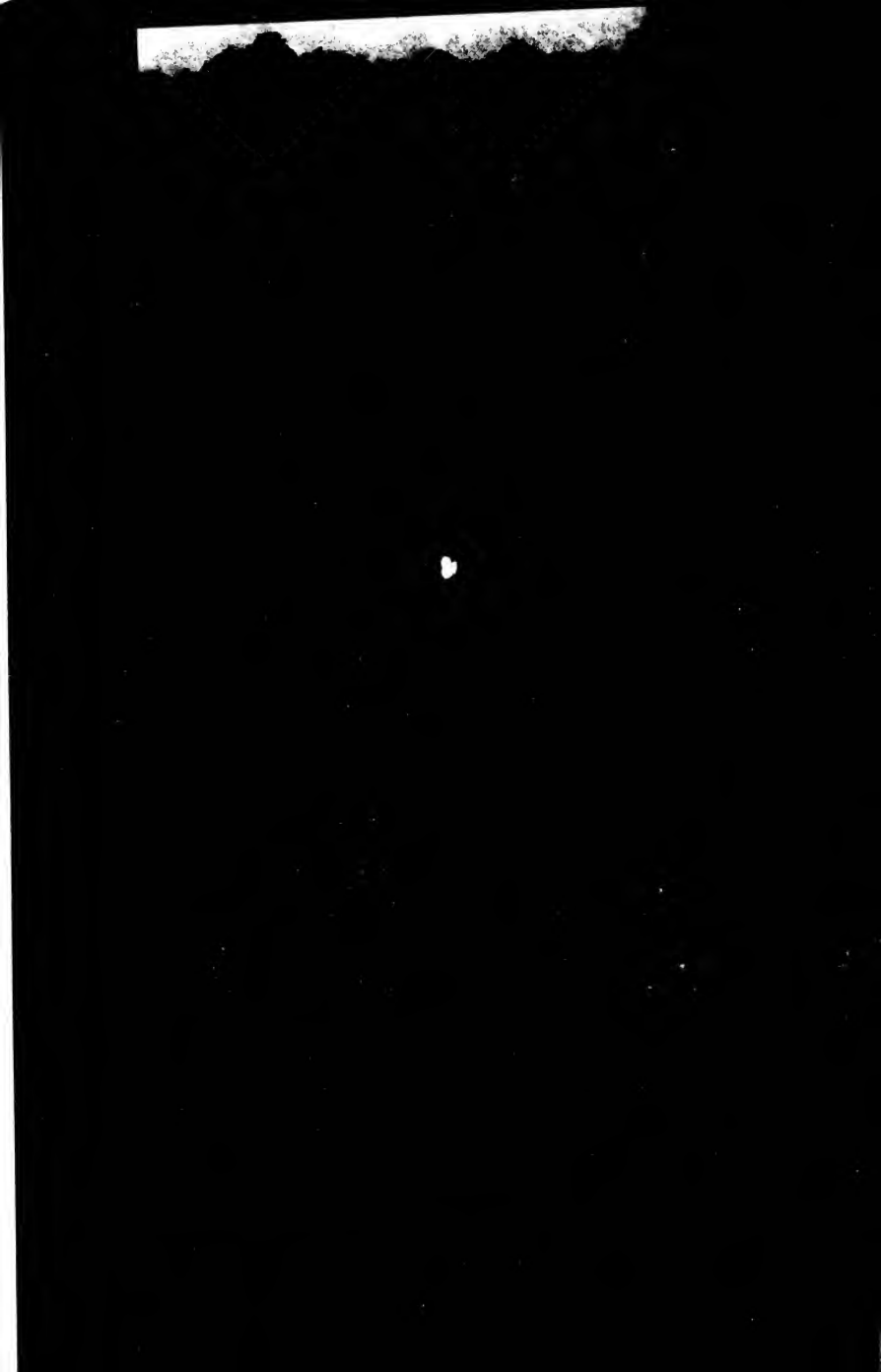

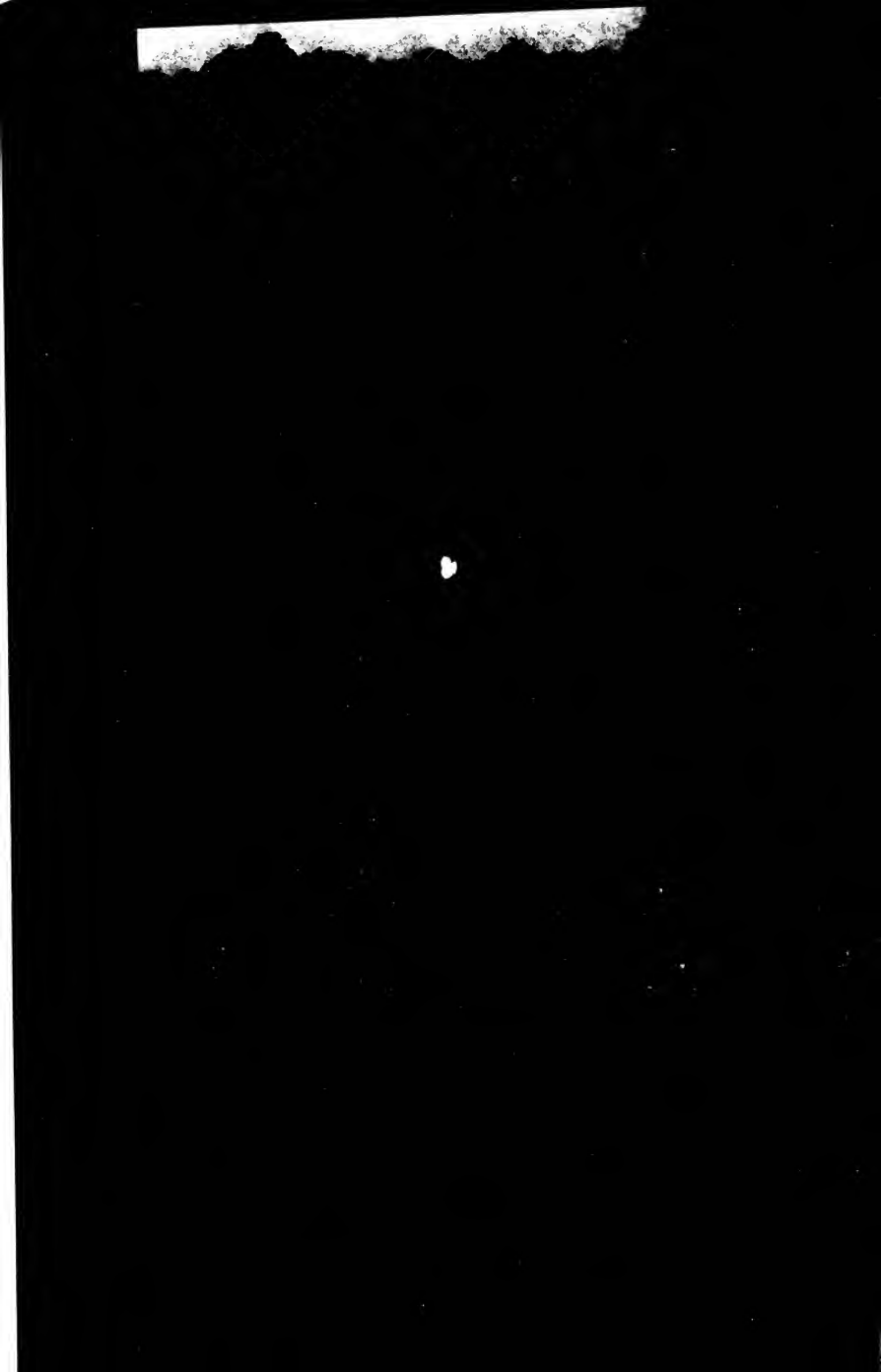

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